Oxidative Reactions of Enolates and Their Application to Total Syntheses of 15-F_{2t}-Isoprostane and Potential Secondary Metabolites of 15-E_2-Isoprostane

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Emanuela Dinca

aus Râmnicu Vâlcea/ Rumänien

1. Referent: Professor Dr. Thomas Lindel
2. Referent: Professor a. D. Dr. Henning Hopf
3. Referent: Professor Dr. Andreas Kirschning
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2. *Total Synthesis of 15-F_{2t}-Isoprostane by Using a New Oxidative Cyclization of Distonic Radical Anions as the Key Step*, U. Jahn, E. Dinca, *Chem. Eur. J.* **2009**, *15*, 58–62.
3. *Toward the Elucidation of the Metabolism of 15-E_2-Isoprostane: The Total Synthesis of the Methyl Ester of a Potential Central Metabolite*, U. Jahn, E. Dinca, *J. Org. Chem.* **2010**, *75,* 4480-4491.
4. *General and Efficient α-Oxygenation of Carbonyl Compounds by TEMPO Induced by Single-Electron-Transfer Oxidation of Their Enolates*, E. Dinca, P. Hartmann, J. Smrcek, I. Dix, P. G. Jones, U. Jahn, *Eur. J. Org. Chem.* **2012**, 4461-4482.

Tagungsbeiträge

1. *The Influence of Enolate Geometry and Aggregate Formation on the Stereoselectivity of Oxidative Enolate Reactions* (Poster – Award for third best poster), E. Dinca, P. Hartmann, U. Jahn, EUCHEM Conference on Organic Free Radicals, 21-25 July 2002, York, United Kingdom.

2. *The Influence of Enolate Geometry and Aggregate Formation on the Stereoselectivity of Oxidative Enolate Reactions* (Oral presentation and poster), E. Dinca, P. Hartmann, U. Jahn, The 2002 Younger European Chemist's Conference, 30 September-3 October 2002, Heidelberg, Germany.
3. *The Influence of Enolate Geometry and Aggregate Formation on the Stereoselectivity of Oxidative Enolate Reactions* (Poster), E. Dinca, P. Hartmann, U. Jahn, ORCHEM 2002, 12-14 September 2002, Bad Nauheim, Germany.

4. *A New Short Approach to the Synthesis of Prostaglandin and Isoprostane Cores* (Poster), E. Dinca, U. Jahn, The 9th International Symposium on Organic Free Radicals, 6-11 June 2004, Porto Vecchio, France.

5. *Eine neue effiziente Methode für die Synthese von Prostaglandin $F_{2\alpha}$ und 15-F_{2t}-Isoprostan und Analoga* (Oral presentation), E. Dinca, Einführungsseminar der Friedrich-Ebert-Stiftung, Februar 2006, Bonn.

6. *Control of Diastereoselectivity in Oxidative Radical Cyclisations and its Application towards a New Synthesis of Prostaglandin $F_{2\alpha}$ and 15-F_{2t}-Isoprostane* (Poster), E. Dinca, U. Jahn, EUCHEM Conference on Organic Free Radicals, 9-13 July 2006, Bergen, Norwegen.

7. *A Short Synthesis of the Full Carbon Skeleton of 15-F_{2t}- and 15-E_2-Isoprostanes by Oxidative Alkoxidoenolate Radical Cyclizations* (Poster), E. Dinca, U. Jahn, Gordon Reasearch Conference "Radicals & Radical Ions in Chemistry & Biology", 1-6 July 2007, Holderness, USA.

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Contents

Abbreviations

BOC	*tert*-butoxycarbonyl
*t*Bu	*tert*-butyl
BuLi	*n*-butyllithium
cat.	catalyst
conc.	concentration
config.	configuration
Cp	cyclopentadienyl
*m*CPBA	*meta*-chloroperoxybenzoic acid
DHA	docosahexaenoic acid
DME	1,2-dimethoxyethan
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
equiv.	equivalents
EPA	eicosapentaenoic acid
Et	ethyl
ET	bis(ethylenedithio)tetrathiafulvalene
EtOAc	ethyl acetate
GC	gas chromatography
HMPA	hexamethylphosphoric amide
IR	infrared spectroscopy
IsoP	isoprostane
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m.p.	melting point
Me	methyl
MS	mass spectrometry
Ms	methanesulfonyl
NeuroP	neuroprostane
OBO	4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl
PG	prostaglandin
Ph	phenyl

PPTS	pyridinium *p*-toluene sulfonate
Pr	propyl
*i*Pr	isopropyl
PRE	persistent radical effect
PUFA	polyunsaturated fatty acids
Py	pyridine
ROS	reactive oxygen species
r.t.	room temperature
SET	single electron transfer
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutyl ammonium fluoride
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidinyl
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
*p*TsOH	*para*-toluenesulfonic acid

1. Introduction

The isolation of complex natural products with interesting biological activities poses many challenges, like accessibility and amount. The chemical synthesis of natural products is the alternative, but a large number of steps, selectivity, time and financial efforts are frequently limiting factors. Nevertheless a synthetic access is often more practical then isolation, since larger amounts can be produced and also more simplified analogs can be obtained using the same strategy. Therefore it is necessary to improve existing synthetic methodologies, and to design new ones. Since most of the natural products are chiral, asymmetric versions of these methodologies must also be developed.

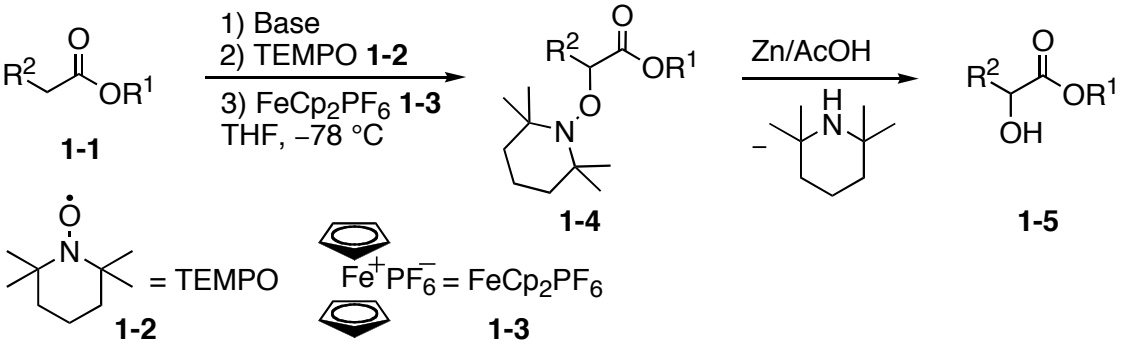
Enolates are important intermediates in the total synthesis of natural products and in organic chemistry in general.[1] They react as carbon-centred nucleophiles in aldol additions, Claisen condensations or alkylations. Asymmetric variants of these reactions are today established synthetic methods.[2] They are also versatile precursors for the α-heterofunctionalisation of carbonyl compounds.[3] Besides reactions with electrophiles, *oxidative reactions of enolate* gained significant importance in the synthesis of different classes of compounds. The oxidative generation of *α-carbonyl radicals* from enolates via *single electron transfer (SET)* was also intensively investigated. They can thus serve as the first intermediates in complex redox reaction sequences.[4]

Single electron transfer (SET) is the generation of a highly reactive intermediate via taking or giving one electron from or to a substrate.[5] SET with a neutral organic molecule generates initially radical ions, while carbanions, radicals and carbocations are linked to each other directly via SET.[5a, c, e] SET at carbonyl compounds can occur either reductively or oxidatively. While reductive SET generates ketyl radical anions at the carbonyl group, oxidative SET acts at the α-position, affording either enol radical cations from neutral substrates or α-carbonyl radicals from enolates. Both are adequately suited to achieve α-functionalisation. Some of the most common SET oxidants[6] used in preparative organic chemistry and especially for carbonyl compounds are $CuCl_2$, $Cu(OAc)_2$, $FeCl_3$,[7] $Fe(acac)_3$, $Mn(OAc)_3$,[8] CAN[9] or ferrocenium hexafluorophosphate. The latter was established as an appropriate SET oxidant for the generation of α-carbonyl radicals from enolates,[10] which is functional group tolerant and recyclable.

The α-heterofunctionalisation of carbonyl compounds gives access to a multitude of building blocks.[3a] Among them, α-hydroxy carbonyl units are prominent motifs, which are common in biologically active natural compounds.[11] Thanks to its coordinating properties, the

hydroxy group located proximal to the carbonyl functionality features the attribute of a directing functional group. Therefore an α-hydroxy carbonyl moiety can be considered as a "privileged synthon".[12] Currently a large number of oxidising reagents for the synthesis of α-hydroxy carbonyl compounds from enolates and silyl enol ethers exist:[13] Oxygen, peroxy reagents, hypervalent iodine reagents,[14] metal oxides, *N*-sulfonyloxaziridines,[13, 15] iodine, ferrocenium hexafluorophosphate or electrochemical oxidation. A large number of methods were developed for the enantioselective synthesis of α-hydroxy carbonyl compounds.[3a, 15, 16] The α-hydroxylation of β-dicarbonyl compounds with oxygen in the presence of catalytic amounts of Ce^{III}-salts was described as an efficient method.[17] Biocatalytic α-oxyfunctionalisation reactions of carbonyl compounds by enzymatic methods were devised.[18] Enol ether and ketene acetal derivatives are adequate prochiral substrates for the synthesis of optically active α-hydroxy carbonyl compounds via the Sharpless dihydroxylation, the enantioselective oxidation by (salen)Mn(III) complexes[19] or by Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in the presence of fructose derivatives.[20] The asymmetric oxidation of acyclic (*Z*)-enol phosphates with Jacobsen's (salen)Mn(III) catalyst afforded α-hydroxy ketones with high enantioselectivity.[21] Another new method is the enantioselective *O*-nitroso aldol reaction of silyl enol ethers.[22]

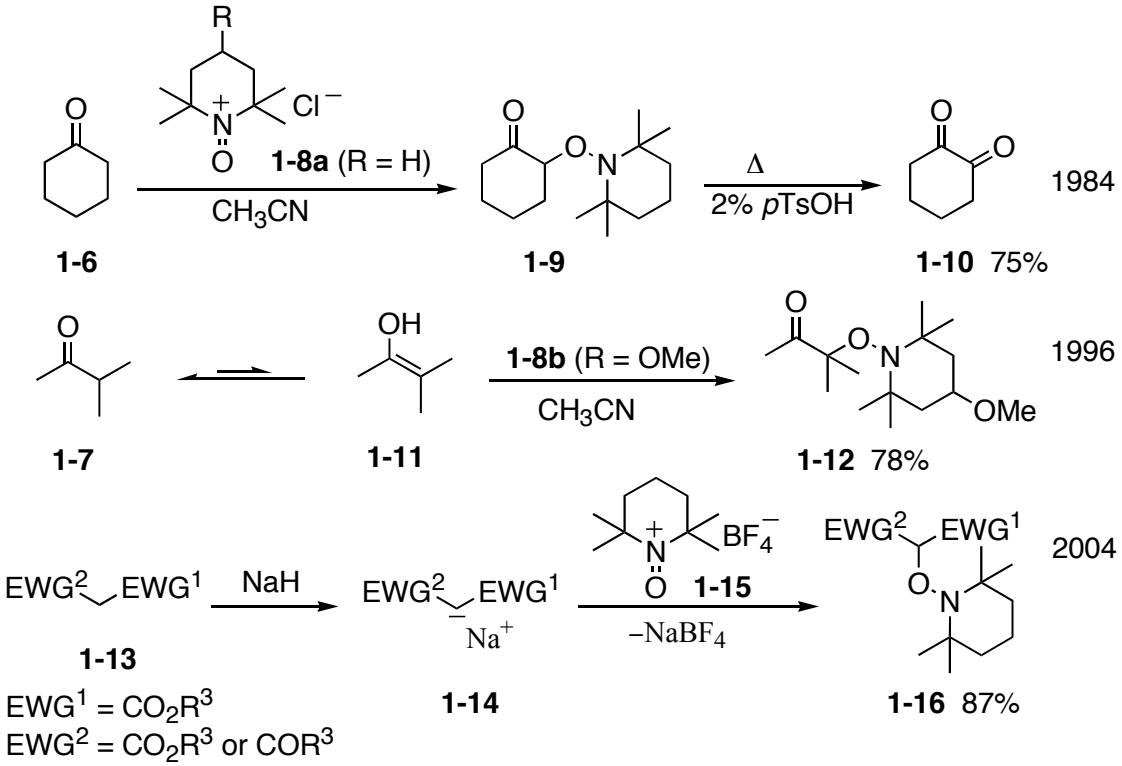
Scheme 1.1 α-Oxygenation of esters with TEMPO



TEMPO-based α-oxygenation reactions of carbonyl compounds. The stable free radical TEMPO **1-2**, which is one of the most common radical scavengers, is a convenient reagent to introduce oxygen in organic molecules.[23] Jahn and Braslau developed the earliest method for the α-oxygenation of esters **1-1** with TEMPO **1-2** almost at the same time (Scheme 1.1).[10a, 24] This consists of generation of the enolate followed by SET oxidation triggered by ferrocenium hexafluorophosphate **1-3**[10a] or by $CuCl_2$[24] to an α-carbonyl radical, which couples with **1-2**. Hartmann and Jahn applied the method also to some amides, ketones and

nitriles.[25] Products **1-4** were reductively deprotected with Zn/AcOH affording hydroxy esters **1-5**.[10a, 26] Alternatively, catecholboron ketone enolates liberate α-carbonyl radicals upon homolytic substitution with **1-2** at boron giving tetramethylpiperidinyloxy-substituted borates. Trapping of the resulting free radical with **1-2** affords aromatic and cyclic α-tetramethylpiperidinyloxy ketones.[27]

Scheme 1.2 α-Oxygenation of ketones and malonates with oxoiminium salts **1-8** or **1-15**

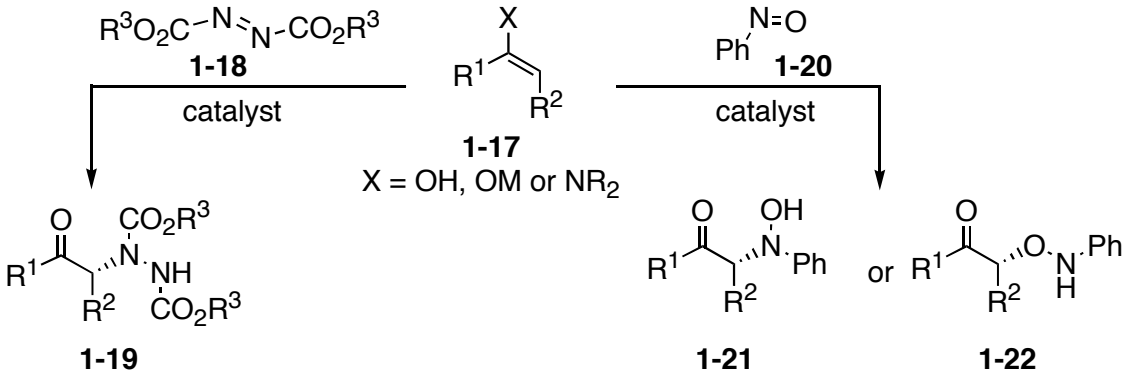


A different oxygenation of enolisable ketones like **1-6** or **1-7** was accomplished by stirring them with 2,2,6,6-tetramethyl-1-oxopiperidinium chloride **1-8a** in acetonitrile (Scheme 1.2).[28] The oxoammonium ion induced probably a single electron oxidation of the enol **1-11** to an enol radical cation, which was trapped by TEMPO **1-2** providing products **1-9** or **1-12** via a free radical mechanism. Compound **1-9** underwent a thermal elimination of tetramethylpiperidine to 1,2-cyclohexanedione **1-10** in 75% yield. Similar α-oxygenations of **1-6** or unsubstituted malonates **1-13** were accomplished by treatment of their enolates, such as **1-14**, with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate **1-15**.[29a] Enaminoesters were oxidised with **1-15** and the mechanism was studied by cyclovoltammetry.[29b]

Organocatalytic oxygenations or *aminations* in the α-position of aldehydes and ketones are currently a tremendously fast developing methodology in organic synthesis.[30] Both can be performed via the nucleophilic addition of an enol(ate) or enamine **1-17** to electrophilic

amination or oxygenation reagents (Scheme 1.3). Azodicarboxylate **1-18** is used widely as a nitrogen source, while nitrosobenzene **1-20** acts either as a nitrogen or as an oxygen source depending on the chosen catalyst affording products **1-21** or **1-22**.[16] These reactions can also be performed in a catalytic and enantioselective manner using Lewis acid or Lewis base catalysis.

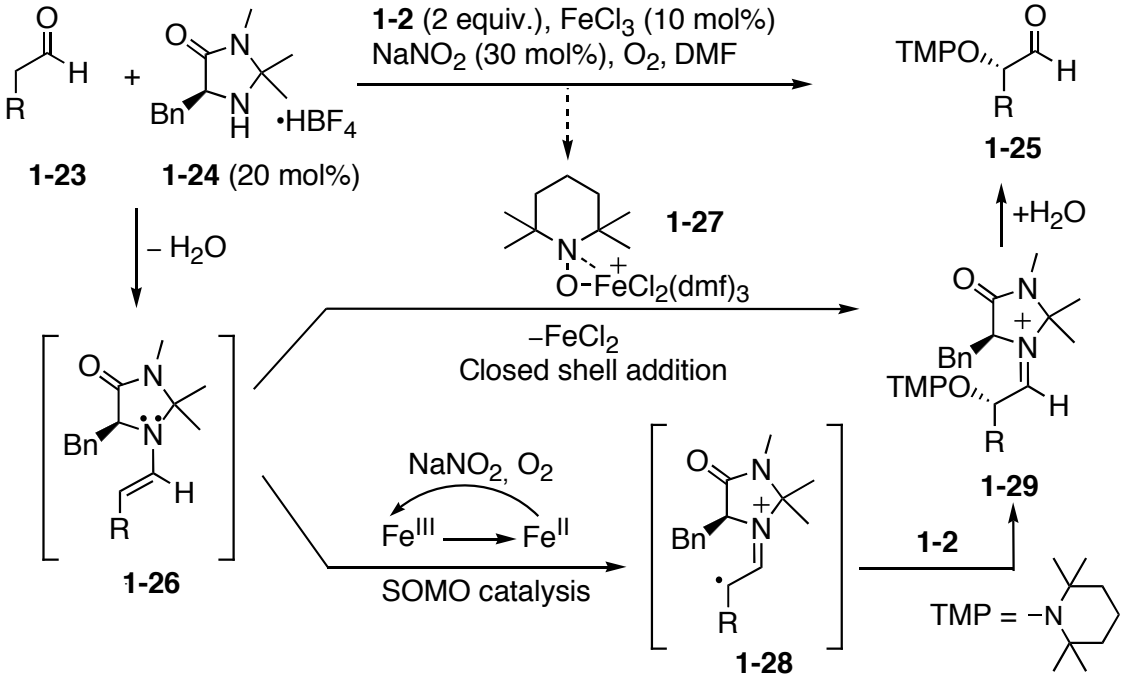
Scheme 1.3 Catalytic enantioselective α-amination and α-oxygenation of aldehydes and ketones



Organocatalytic α-hydroxylations of ketones using oxidants, such as iodosobenzene and *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine, in the presence of *L*-proline or proline amines as catalysts were developed.[31] The oxidation of 2-alkoxycarbonylindanone and other β-keto esters with cumyl hydroperoxide catalysed by chiral dihydroquinines is suitable for the direct introduction of hydroxy groups.[32] Aldehydes and cyclic ketones were also hydroxylated with singlet molecular oxygen and excitation by UV light in the presence of tetraphenylporphyrin or *L*-proline in the presence of α-methylproline.[33] Another organocatalytic oxygenation method is the asymmetric benzoyloxylation of aldehydes.[34]

New organocatalytic approaches to the enantioselective α-oxygenation of aldehydes **1-23** using TEMPO **1-2** as the oxygen source were developed by Sibi's group (Scheme 1.4).[35] They used MacMillan's imidazolidinone catalyst **1-24** and different iron-based SET reagents to generate the crucial radical **1-28**. Based on the evidence, a radical-catalytic cycle (Single-Occupied Molecular Orbital (SOMO)-catalysis) was proposed to operate. Initially formed enamine **1-26** was oxidised to radical cation intermediate **1-28**, which was trapped by **1-2**. The resulting iminium ion **1-29** was hydrolysed to product **1-25**, releasing catalyst **1-24**. A later study concluded that this transformation should proceed predominately via a closed shell addition of TEMPO-$Fe^{+}Cl_2(dmf)_3$ complex **1-27** to the enamine **1-26**.[36] At present, the experimental evidence provided is not sufficient to distinguish closed shell and SOMO-enamine activation mechanisms conclusively.

Scheme 1.4 Enantioselective α-oxygenation of aldehydes **1-23** with **1-2**



Sibi's methodology flourished recently and a number of asymmetric α-oxygenations of aldehydes by **1-2** using chiral pyrrolidine catalysts and anodic oxidation[37] or resin-supported peptide catalysts in aqueous media and chemical oxidation were published.[38] Maruoka et al. replaced the metal SET oxidant by benzoyl peroxide, which oxidises TEMPO **1-2** in situ to oxoammonium ion **1-15**.[39] Using different chiral pyrrolidines or binaphthyl-based secondary amines as catalysts, compounds of type **1-25** were synthesised with high enantioselectivities.

Another new catalytic method for the synthesis of α-(2,2,6,6-tetramethylpiperidinyloxy) carbonyl compounds is the photocatalysed α-oxygenation of aromatic β-keto esters or aldehydes with TEMPO via irradiation with visible light in the presence of organic dyes.[40]

*Oxygenation by TEMPO **1-2** as a termination step in reaction sequences.* Highly valuable and relatively new applications of TEMPO **1-2** are reaction sequences, which combine a free radical 5-*exo* cyclisation followed by trapping of the cyclised radical with TEMPO. Recently, syntheses of substituted pyrrolidines via an oxidative tandem anionic-radical methodology were reported,[4e, 41] which consists of conjugate addition of lithium *N*-allylic amides to α,β-unsaturated esters, SET oxidation of the resulting enolate by **1-3**, radical 5-exo cyclisation and finally trapping of resulting cyclic radical with **1-2**. *N*-Protected 4-oxymethylpyrrolidine-3-carboxylates were obtained in moderate to good yields with exclusive 2,3-*trans* selectivity and variable 3,4-diastereoselectivity. Aryl radicals generated from aryl iodides with Bu_3SnH add intramolecularly in a 5-*exo* cyclisation mode to a double bond with

subsequent TEMPO trapping. This method was used in the total synthesis of natural products.[26a, 42] The carboaminohydroxylation of olefins with aryl diazonium salts, $FeSO_4$ and TEMPO gave access to aromatic α-(2,2,6,6-tetramethylpiperidinyloxy) carboxylic acid derivatives by an aryl radical addition/oxygenation sequence.[43] Recently, a highly stereoselective synthesis of 1,2,3-substituted indanes from 3-substituted indenes via a palladium-catalysed carboaminoxylation with arylboronic acids and TEMPO was developed.[44] Cyclisations of α-substituted 4-pentenyl sulfonamides, which are catalysed by $Cu(ET)_2$ or $Cu(OTf)_2$ in the presence of Cs_2CO_3, followed by oxygenation with TEMPO afforded cyclised aminoxylated sulfonamides in good yields and high *cis*-diastereoselectivity.[45]

Several alkoxyamines, such as **1-16**, served as precursors for thermal radical addition or cyclisation reactions, in which oxygenation by TEMPO **1-2** serves as the termination step. These methods are based on the *persistent radical effect* (PRE).[23b, 46] This explains the selective formation of the radical cross-coupling product, when both a transient C-centred radical and a persistent radical are generated via a C-O bond homolysis from alkoxyamines at equal rates. The persistent radical TEMPO does not dimerise, while the transient C-centred undergoes in the very beginning some homocoupling or disproportionation reactions to a small extent, which led to a slightly increased concentration of the nitroxyl radical. Based on this concentration imbalance, the cross-coupling of the persistent and transient radical will occur selectively and any further self-termination of transient radicals does not compete anymore in the further course. The PRE was applied in thermal radical carboaminoxylation of alkenes, PRE-controlled malonate alkoxyamine additions and addition/cyclisation reactions of alkoxyamines with alkenes.[23, 46a-c] Alkoxyamines were also used as initiators and mediators for controlled (or living) radical polymerisations.[23, 46d, 47] Nitroxide-mediated polymerisations (NMP) allow the preparation of polymers with defined molecular weight using the PRE. The reversible C-O bond homolysis generates a nitroxide persistent radical and a chain-growing polymer radical, which will be extended by monomer insertion and reversible trapping by the persistent nitroxide.

TEMPO as an oxidant. Catalytic oxidations using the organocatalyst TEMPO and its derivatives alone or together with metal salts found numerous applications.[48] Hydrogen atom abstraction by TEMPO **1-2** in allylic positions is difficult, it occurs only at high temperatures and using the substrate as the solvent.[49] Allylic oxidations of substituted olefins with in situ from **1-2** generated oxoammonium salt **1-15** ($TEMPO^+BF_4^-$) in aqueous acetonitrile giving α,β-unsaturated ketones was reported to be more efficient.[50] The reaction occurred probably

via hydride abstraction and trapping of the generated allylic cation with water. Subsequent oxidation of the resulting allylic alcohol by the oxoammonium salt afforded the α,β-unsaturated ketone. TEMPO **1-2** is able to abstract hydrogen atoms from phenols.[51a-c] The antioxidant properties of phenols were analysed using a chromophore-conjugated TEMPO derivative, which is nonfluorescent. The TEMPO-derivative becomes fluorescent upon reduction to the TEMPO-H derivative, allowing to determine the kinetics of the H-transfer process. Hydrogen abstraction from hydroxylamines[51d] or silanes[51e] also succeeds. A peculiar carbene-catalysed oxidation of aldehydes by TEMPO leading to 1-(Acyloxy)-2,2,6,6-tetramethylpiperidines was reported by Studer.[52]

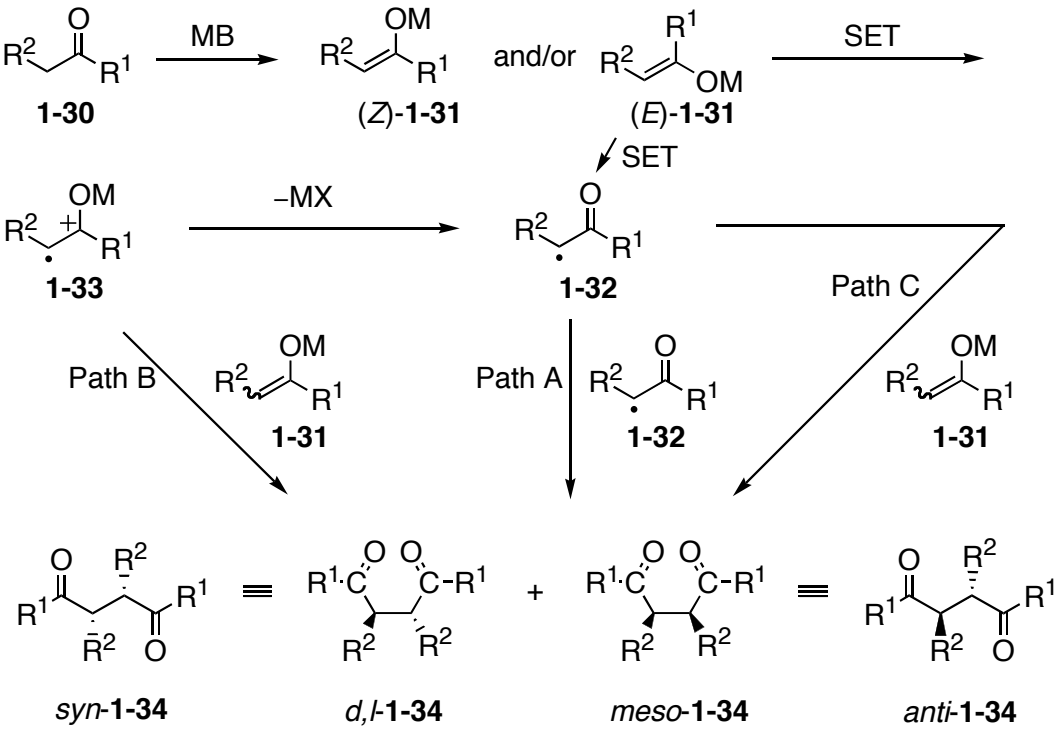
TEMPO **1-2** oxidises organometallic compounds to carbon-centred radicals, which are subsequently trapped by a second equivalent of TEMPO affording alkyl alkoxyamines. Different alkyl metal compounds (lithium, magnesium, zirconium, copper, zinc) were oxidised with 2 equivalents of TEMPO giving the corresponding alkoxyamines.[23, 53] Alkyl catecholboranes afforded alkoxyamines upon reaction with **1-2** similarly.[54, 55] TEMPO was also employed as a terminal oxidant in transition metal-catalysed polar coupling reactions, such as copper-catalysed cross-coupling reactions of amines or phenols with arylboronic acids,[56] rhodium-catalysed homocouplings of various alkenyl and arylboronic acids,[57] rhodium-catalysed cross-couplings of arylboronic acids with arenes and heteroarenes,[58] or palladium-catalysed C-H arylations of 2-phenylpyridine with various boronic acids.[59]

1,4-Dicarbonyl compounds are versatile building blocks for the synthesis of natural products, heterocycles and 1,4-diols. The nucleophilic substitution of α-halo ketones by enolates has been so far the most common synthetic approach to 1,4-diketones. This method had, however, a very limited scope. Recently C-C bond formation between the α-positions of two carbonyl compounds gained more interest. New efficient methods for the synthesis of unsymmetrical 1,4-diketones by such methods are the coupling of α-chloro ketones with tin ketone enolates catalysed by $ZnCl_2$[60] or palladium-catalysed cross-couplings of substituted α-chloro ketones with zinc ketone enolates for the construction of 2,3-diaryl-1,4-diketones.[61]

Dimerisations of enolates allow the fastest assembly of 1,4-dicarbonyl compounds.[62] This process usually involves the oxidation of the enolate to α-carbonyl radicals via SET using salts of Cu(II), Ti(IV) and Fe(III), iodonium salts, molecular iodine as oxidants or electrolysis, followed by the coupling of these radicals (Scheme 1.5). The earliest experiments included oxidative dimerisations of *t*-butyl acetate and ketone enolates induced by Cu(II) salts, affording di-*tert*-butyl succinate and 1,4-diketones.[63] The enolates of some cyclic

ketones underwent oxidative dimerisation with $FeCl_3$ in 23-69% yield with low diastereoselectivity.[64] *p*-Tolylbiphenyl-2,2'-ylenebismuth bis(trifluoromethanesulfonate) was used as an alternative oxidant for the oxidative dimerisations of ketones, esters and thioesters.[65] The diastereoselectivity was not discussed. Recently a two-step one-pot method for the preparation of 1,4-dicarbonyl compounds was reported, which consist of a cerium-catalysed C-C radical addition of styrene with 1,3-dicarbonyl compounds followed by Kornblum-De La Mare fragmentation.[17b]

Scheme 1.5 Oxidative homocoupling of enolates



Simple diastereoselectivity was observed only sporadically in oxidative dimerisations. Titanium enolates of phenylacetate were oxidatively coupled in the presence of $TiCl_4$ and Et_3N. The highly selective formation of *d,l*-2,3-diphenylsuccinic acid dimethyl ester was attributed to the oxidation of Ti-bridged enolate dimers.[66] This method is however limited to this substrate. Carboxylic acid dianions dimerised with a low *meso/d,l* diastereoselectivity on oxidation with iodine.[67] The coupling of fatty acid methyl ester enolates induced by $CuBr_2$ occurred mostly unselectively.[68] The oxidative coupling of the enolate of (1*R*)-(+)-verbenone was studied with $CuCl_2$ and $FeCl_3$.[69] The regioselectivity was examined in this case. Asymmetric dimerisations were accomplished only for carboxylic acid derivatives, which were bound to chiral auxiliaries.[70] A dimerisation of the enolate of Seebach's proline-derived oxazolidinones with vicinal dihalides, and subsequent hydrolysis of the oxazolidine ring

afforded (*R,R*)-α,α'-biproline and *meso*-α,α'-biproline.[71] Silyl ketene acetals were dimerised to substituted succinates using $TiCl_4$ (61%) or $FeCl_3$ (14%).[72] A high *d,l* diastereoselectivity was achieved by Schmittel et al. for the intramolecular dimerisation of silicon bisenolates of propiophenone.[73] The oxidative coupling was induced by $[Fe(phen)_3](PF_6)_3$ or CAN.

In the last decade, intermolecular couplings of different types of carbonyl compounds gained much interest. Thomson et al. employed the cross-coupling of unsymmetrical silyl bis-enol ethers, induced by CAN, for the synthesis of 1,4-diketones derived from tetralone, indanone and cyclohexanone.[74] Baran and coworkers studied the oxidative coupling of ketones with *N*-acyl oxazolidinones and oxindoles, using Fe(III) and Cu(II) salts.[75] The enantioselective synthesis of α-substituted γ-keto aldehydes from α-substituted aldehydes and enol silanes was developed using an organocatalytic SOMO activation protocol.[35b, 76]

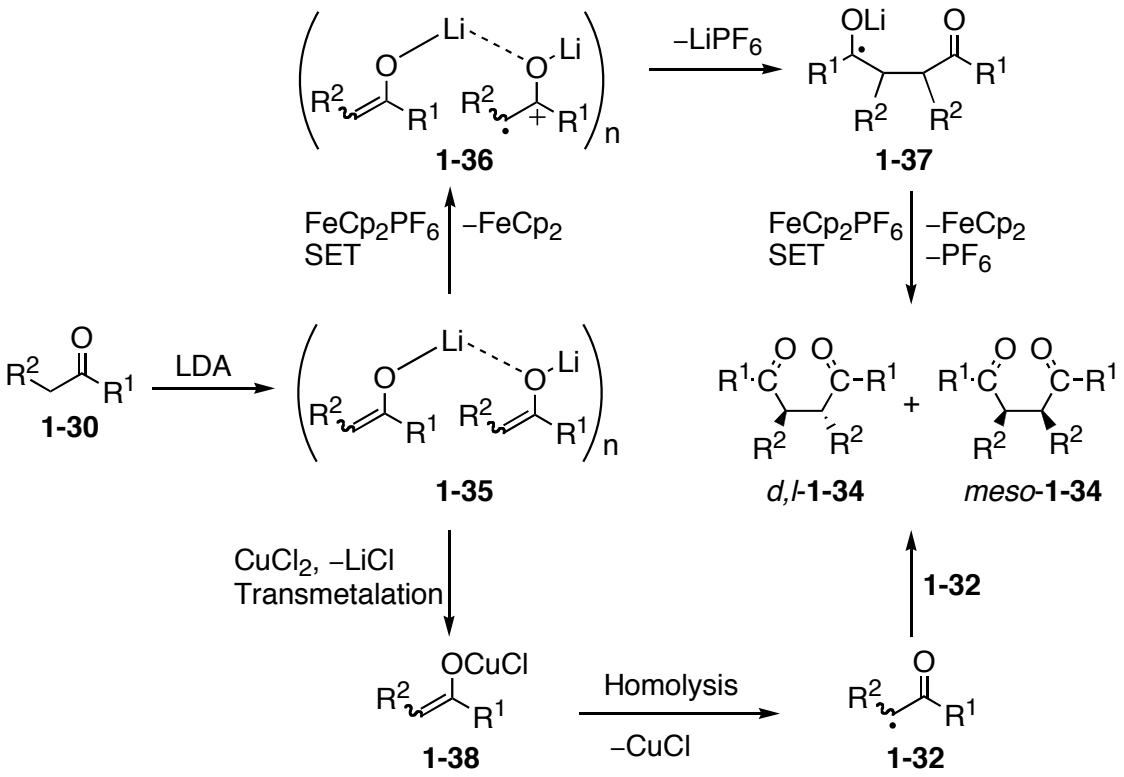
Applications in total syntheses of natural products emerged both for homo- and hetero-couplings of enolates. Some intramolecular oxidative dimerisations of ketone enolates with $CuCl_2$ were applied in total syntheses of C_{16}-Hexaquinacene and cerorubenic acid-III.[77] The syntheses of the central ring of Lomaiviticin A[78] and of (–)-Bursehernin[79] were recently reported.

The mechanism of oxidative homocouplings and heterocouplings was so far not elucidated in depth (Scheme 1.5, only homocouplings shown).[62] Rathke proposed a radical-radical coupling mechanism of **1-32** resulting from oxidation of enolate **1-31** (Path A) to the products *d,l*- and *meso*-**1-34**.[63a] Schmittel considered the stability of the M-O bond of high importance.[73] The non-diastereoselective dimerisation of titanium bisenolates was depicted as an intermolecular process, which occurred via addition of the titanium radical cation **1-33** to the enolate **1-31** after Ti-O bond cleavage (Path B). A third possibility (Path C) is the interaction of the SOMO of the radical **1-32** with the HOMO of the enolate **1-31** in a formal radical addition.

An important aspect is that the exact role of the metal oxidant in dimerisations is most often not known. Inner-sphere or outer-sphere oxidants may react differently and can lead to different diastereoselectivities.[25] Jahn et al. introduced ferrocenium hexafluorophosphate **1-3** as a versatile recyclable SET oxidant for the generation of α-carbonyl radicals from enolates (Scheme 1.6).[10a, 25] They developed an efficient method for oxidative dimerisations of esters and propiophenone enolates, induced by **1-3**. Moderate diastereoselectivity *meso/d,l* = 2:1 were obtained for some esters. Propiophenone displayed high *d,l/meso*-diastereoselectivities of 10:1. The results were rationalised from a new perspective. On one hand a correlation between the enolate geometry[80] and the stereochemistry of the major diastereomer was

observed. On the other, it was postulated that the reaction outcome was strongly determined by the mechanism of oxidation and enolate aggregation.[81] Deprotonation of carbonyl compound **1-30** under different conditions generates enolate aggregates **1-35**, in which the enolate unit may have (*E*)- or (*Z*)-geometry. The oxidation with ferrocenium hexafluorophosphate **1-3** occurred probably via outer-sphere electron transfer, leading to an α-carbonyl radical, which remains bound in the aggregate **1-36**. Radical addition giving **1-37**, followed by a second SET, leads to the products **1-34** with different diastereoselectivities. The oxidation of **1-35** with $CuCl_2$ occurred in contrast probably via an inner-sphere electron transfer. Transmetallation of Li with Cu lead to the monomeric enolate **1-38**, which homolysed to α-carbonyl radical **1-32**. Radical coupling of two **1-32** units afforded compounds **1-34** in a 1:1 *meso:d,l* ratio.

Scheme 1.6 Dimerisation of carbonyl compounds

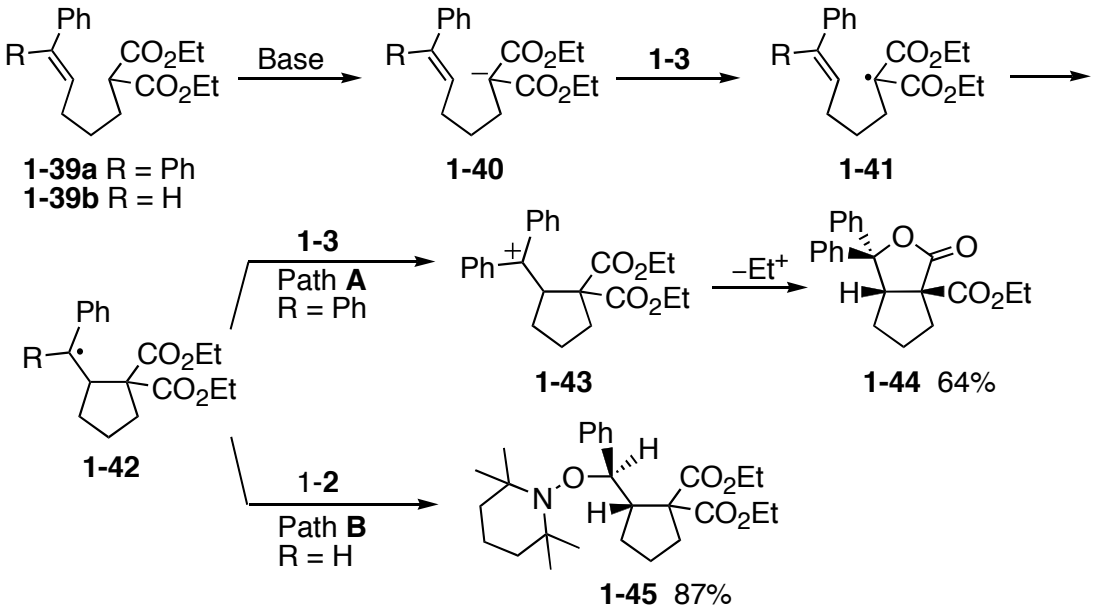


5-exo Radical cyclisations based on SET oxidations of enolates

Radical cyclisations are intramolecular kinetically controlled radical additions to multiple bonds.[5a, 6, 82] They are a fundamental method for the synthesis of cyclic organic compounds. Their advantages consist of high predictability and functional group tolerance. The most popular are 5-hexenyl radical cyclisations. The stereoselectivity of 5-*exo* radical

cyclisations can be predicted and rationalised by means of the Beckwith-Houk transition state model.[83]

Scheme 1.7 Oxidative 5-*exo*-cyclisation of substituted malonates **1-39**



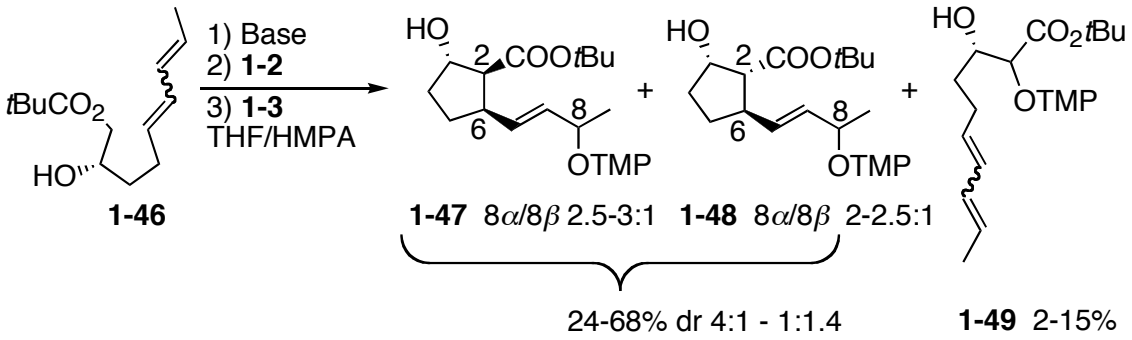
Oxidative 5-*exo* cyclisation of substituted malonate enolates[10b, c, 84] marked the beginning of a new methodology, which combines anionic and radical processes in reaction sequences with intermediates of different oxidation states (Scheme 1.7). Enolates **1-40**, generated from **1-39** by deprotonation with LDA, proved to be adequate precursors for radicals **1-41**. SET oxidation of **1-40** using ferrocenium hexafluorophosphate **1-3** afforded α-carbonyl radicals **1-41**, which underwent a 5-*exo* radical cyclisation. The cyclic radicals **1-42** were further oxidised to carbocations **1-43** if R = Ph (Path A), which lactonised, giving products **1-44** in 64% yield. In the presence of TEMPO **1-2** (Path B), radicals **1-42** (R = H) were trapped to oxygenated product **1-45** in 87% yield. Thus malonate enolates are convenient starting materials for radical reactions and reaction sequences, which are induced by the SET oxidant **1-3**.

Total syntheses of lipid metabolites

Based on the oxidative cyclisation of substituted malonates, model studies were performed on oxidative radical cyclisations of **1-46** (Scheme 1.8).[85] Hydroxy ester **1-46** was twofold deprotonated and the resulting dianion underwent an oxidative radical cyclisation induced by **1-3**, which was terminated by trapping with **1-2**. This cascade reaction afforded

cyclopentanes **1-47** and **1-48** as main products, accompanied by small amounts of **1-49** and other diastereomers. The advantage is on one hand that it allowed access to the cyclopentane core structures **1-47** with isoprostane relative ring configuration (2,6-*cis*) and **1-48** with prostaglandin ring configuration (2,6-*trans*), respectively. On the other hand, trapping by **1-2** allowed the introduction of a protected oxygen functionality in the distal 8-position in both ring diastereomers.

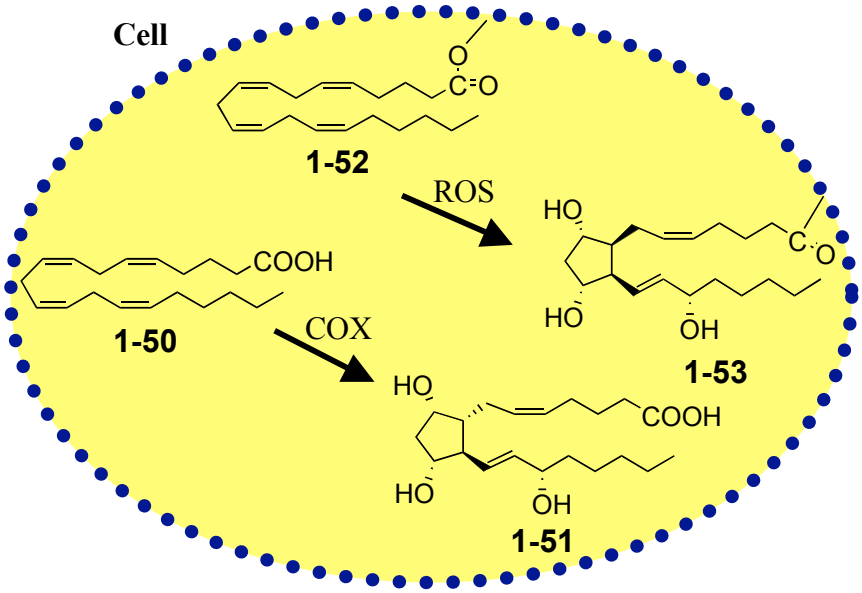
Scheme 1.8 5-*exo*-Radical cyclisation of hydroxy ester **1-46**



The further development of similar radical cyclisations would provide the basis for the total synthesis of functionalised cyclopentanes, such as prostaglandins, isoprostanes and neuroprostanes, which are significant metabolites formed *in vivo* in humans from polyunsaturated fatty acids.[86] Similar metabolites found in plants are the phytoprostanes or jasmonic acid.

Arachidonic acid **1-50** is one of the most important polyunsaturated fatty acid. It occurs to a large extent as a component of the cell membrane and is the substrate for a variety of biologically active natural products.[87] The enzymatic transformation of free **1-50** gives prostaglandins, thromboxanes and leukotrienes (Figure 1.1).[88] They are local hormones, which are biosynthesised on demand and quickly metabolised after fulfilling their functions. The biosynthesis of enantiomerically pure prostaglandins (PG) **1-51** consists of exclusive hydrogen abstraction at 13-position, followed by a free radical cascade of peroxidation, double 5-*exo* cyclisation, oxygenation and final reduction inside the cyclooxygenase enzymes. The non-enzymatic autoxidative metabolism of membrane- or low-density lipoprotein (LDL)-bound arachidonic acid **1-52** leads to the formation of a large number of regioisomeric oxygenated metabolites including the isoprostanes (IsoP) **1-53**, which are diastereomers of PG.[86, 89] The IsoP biosynthesis starts also with hydrogen abstraction, this time at any one of the three bisallylic positions induced by reactive oxygen species (ROS). A similar free radical cascade follows, leading to formation of a racemic mixture of IsoP regioisomers **1-53**.

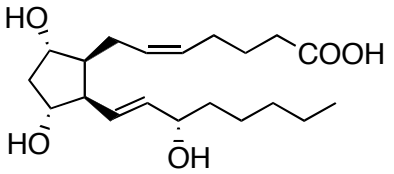
Figure 1.1 Schematic depiction of the formation of $PGF_{2\alpha}$ **1-51** from free arachidonic acid **1-50**, and of 15-F_{2t}-IsoP **1-53** from membrane-bound arachidonic acid **1-52** within the cell (only one regio- and stereoisomer of IsoP shown).



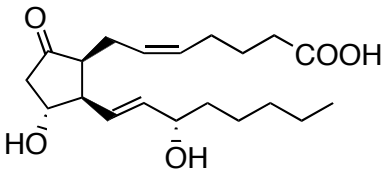
COX = Cyclooxygenase enzyme
ROS = Reactive oxygen species

The most significant structural difference between PG and IsoP is the spatial arrangement of the alkyl side chains. In PG the alkyl chains at the cyclopentane ring are oriented *trans* to each other, enforced by the spatial constraints of the enzyme. The cyclopentane ring of IsoP is formed by a free radical 5-*exo* cyclisation, which proceeds kinetically controlled via a Beckwith-Houk transition state. Therefore the alkyl chains in isoprostanes are oriented *cis* to each other.

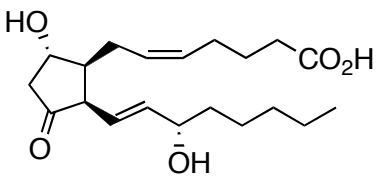
Figure 1.2 The 15-series of different ring-substituted isoprostanes



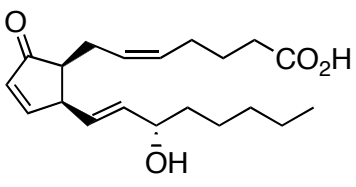
15-F_{2t}-IsoP **1-54**



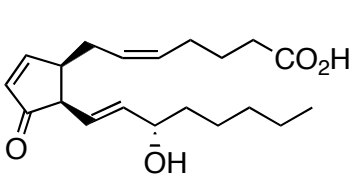
15-E_2-IsoP **1-55**



15-D_2-IsoP **1-56**



15-A_2-IsoP **1-57**



15-J_2-IsoP **1-58**

Initial hydrogen abstraction at 7-position gives the 5-IsoP series, at 10-position the 8-IsoP and 12-IsoP series, while hydrogen abstraction at the 13-position leads to the 15-IsoP series. The ring substitution patterns can be different within each series (Figure 1.2). For example in the presence of high levels of reducing agents in the cell, the formation of 15-F_{2t}-IsoP **1-54** is preferred. However, formation of 15-E_2-IsoP **1-55**, 15-D_2-IsoP **1-56**, 15-A_2-IsoP **1-57** and 15-J_2-IsoP **1-58** dominates when the cell lacks sufficient amounts of reducing equivalents.

Prostaglandins regulate a multitude of functions: They stimulate inflammatory reactions and are pain mediators, regulate the blood pressure, control the transportation of ions through the cell membrane, modulate the synaptic transmission or induce sleep. Isoprostanes caught the attention as Robert and Morrow discovered in 1990 that these compounds were produced *in vivo* in considerably larger amounts than prostaglandins. Since then an intense research effort was made to unravel the biological functions of these metabolites.[86, 89b] A large variety of health disorders like cardiovascular, renal, pulmonary, liver and neurological diseases are correlated with oxidative stress, which increases the levels of F_2-IsoP. *Oxidative stress* occurs when the concentration of ROS increases due to imbalances of the redox state of cells or tissues. This induces a cascade of oxidative and free radical damage of all susceptible molecules, especially lipids. Thanks to their stability F_{2t}-IsoP are used today as the gold standard for quantifying oxidative stress. There is a confirmed relationship between F_2-IsoP levels and the severity of heart failure. Oxidative stress is involved in the early development of atherosclerosis. Different exogenous factors like smoking, drug treatment, alcohol consumption, and dietary antioxidant supplementation increase the F_2-IsoP concentrations in blood. F_2-IsoP levels are positively correlated to these factors and therefore quantification of F_2-IsoP represents a physiological marker of oxidative stress. They represent a tool for the assessment of oxidative stress in antioxidant therapies. The quantification of F_2-IsoP metabolites in urine is a non-invasive method to assess the oxidative stress in vivo.

To study their biological functions and to further develop new methods for diagnostic applications, IsoP must be available in sufficient amounts. A large number of total syntheses of cyclic PUFA metabolites was published, but they concern only a few members from the vast number of IsoP, such as 15-F_{2t}-IsoP. The known total syntheses were recently comprehensively reviewed by Jahn et al.[86a] and classified in three categories based on the employed strategies: Biomimetic approaches (cyclisation of full-chain precursors), chain

attachments to cyclopentane cores and cyclisation reactions followed by chain attachment. A few total syntheses published more recently are highlighted here.

Taber et al. prepared four enantiomerically pure 13-F_{4t}-NeuroP diastereomers by a new biomimetic methodology, based on a highly diastereoselective thermal intramolecular ene cyclisation, which gives potentially access to any isoprostane or neuroprostane.[90]

Starting with an enantioselective pure diol derived from Corey's lactone, Rokach et al. synthesised 5-*epi*-8,12-*iso*-IsoP $F_{3\alpha}$ and 8,12-*iso*-IsoP $F_{3\alpha}$, derived either from autoxidation of eicosapentaenoic acid or from β-oxidation of DHA-derived neuroprostanes.[91] Using synthetic probes, they discovered both molecules in human urine. The quantification of these IsoPs may be useful to assess the oxidative damage of EPA- and DHA-containing phospholipids. A similar strategy was used by Helmchen et al. who employed a diol derived from Corey's lactone, enantiomeric to Rokach's diol as starting material for total syntheses of *ent*-5-F_{2c}-IsoP and 5-*epi*-ent-5-F_{2c}-IsoP.[92] 5-F_{2c}-IsoP belongs to the most often found IsoP in human urine. The key step consists of introduction of the side chains by an (*E*)-selective Horner-Wadsworth-Emmons reaction.

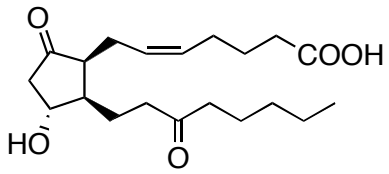
Jung et al. prepared 1-palmitoyl-2-(5,6)-epoxyisoprostane E_2-*sn*-glycero-3-phosphocholine (PEIPC) efficiently from 2-bromo-4-(arylmethoxy)cyclopentenone.[93] This E_2-IsoP derivative is especially active in inflammatory responses connected to atherosclerosis.

Applying regioselective intermolecular Pauson-Khand reactions of silyloxymethyl alkynes, Riera and coworkers synthesised protected (hydroxymethyl)cyclopentenones with the attached α-chain, which were transformed to the corresponding aldehydes.[94] Subsequent Julia olefinations with the chiral ω-chains provided phytoprostane B_1 type I and prostaglandin B_1. A new short synthesis of enantiopure phytoprostanes B_1 commencing with a (dimethoxyphosphoryl)methyl-substituted cyclopentenone was accomplished by Mikolajczyk.[95] The side chains were attached by an alkylation and a Horner reaction. Durand et al. accomplished recently syntheses of the enantiopure diastereomers of phytoprostanes E_1 type II and 15-E_2-isoprostanes.[96] The enantiopure precursor 4-hydroxy-2-cyclopentenone was obtained by regioselective fragmentation of a furan derivative, followed by subsequent cyclisation and enzymatic kinetic resolution. The side chains were attached by Horner-Wadsworth-Emmons and Wittig reactions, respectively.

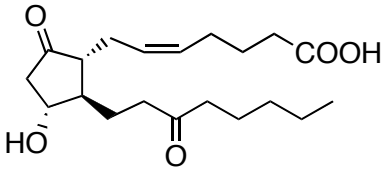
Eight enantiomerically pure 5-F_2-IsoPs were prepared in 10 steps using a stereodivergent route from a functionalised bicyclo[3.2.0]heptene by Snapper et al.[97] The key feature of the strategy was its ring-opening cross-metathesis with ethylene, followed by a cross-metathesis of the resulting diene with an enone.

Galano and Durand developed a conceptually new stereocontrolled strategy, which is based on a α,β-epoxy ketone prepared from a hydroxy bicyclo[3.3.0]octene by stereoselective epoxidation.[98] The side chains were introduced via ozonolysis. New total syntheses of 15-F_{2t}-IsoP, 15-*epi*-15-F_{2t}-IsoP, 15-*epi*-15-E_2-IsoP and [D_4]-labelled F_{4t}-neuroprostane as well as the first synthesis of 15-D_{2t}-IsoP were accomplished.

Figure 1.3 Potential metabolites of 15-E_2-IsoP **1-55**



13,14-Dihydro-15-oxo-E_2-IsoP **1-59**



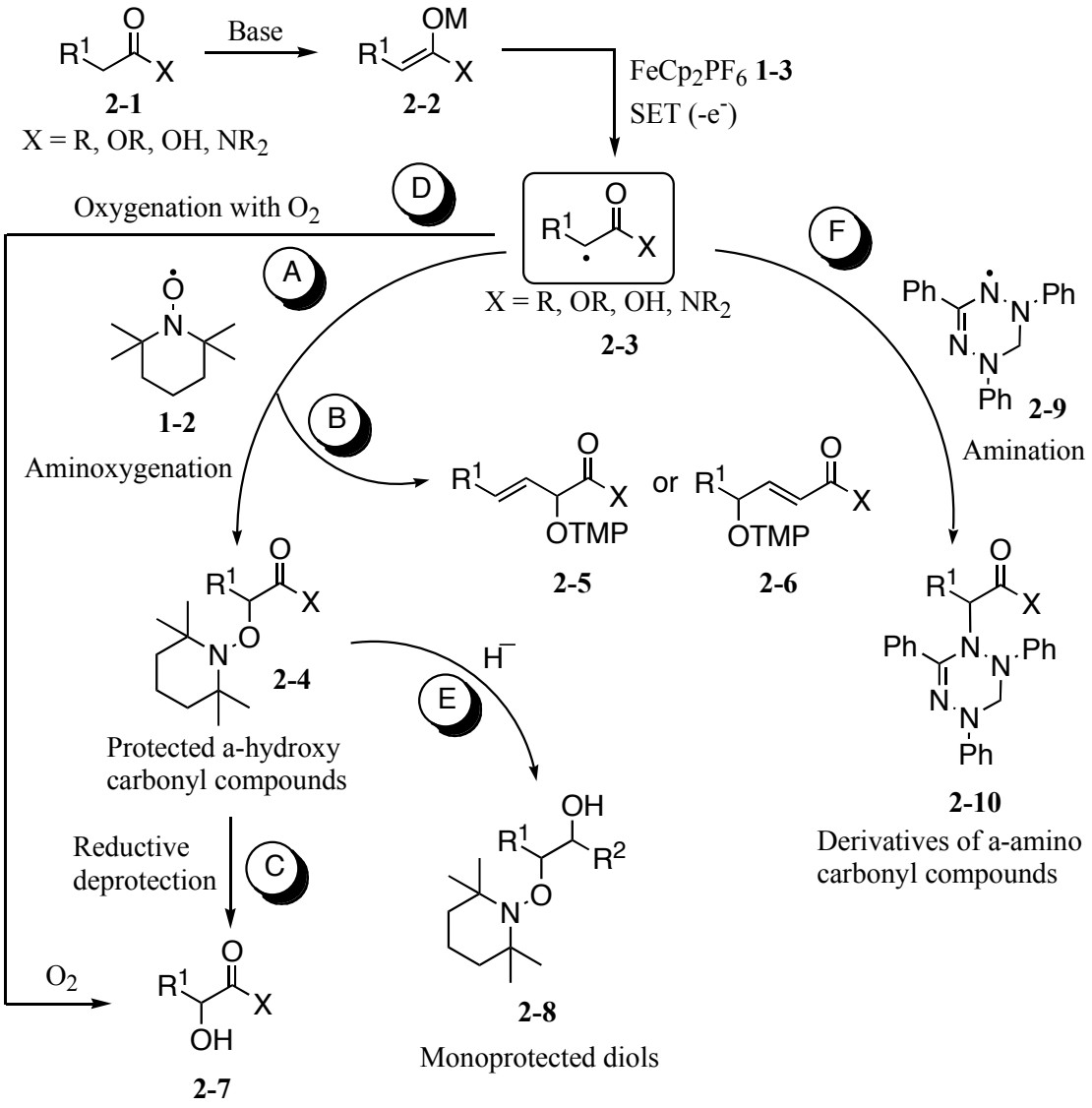
13,14-Dihydro-15-oxo-PGE_2 **1-60**

Although a large number of total syntheses of 15-F_{2t}-IsoP **1-54** and a few of 15-E_2-IsoP **1-55** exist, a need for more efficient strategies offering shorter and higher-yielding syntheses to deliver sufficient amounts of isoprostanes is obvious. The metabolism of most IsoPs except 15-F_{2t}-IsoP **1-54** is not known. Approaches to potential metabolites like racemic **1-59** and **1-60** will help to unravel the metabolic pathways of 15-E_2-IsoP **1-55** (Figure 1.3). Syntheses of **1-59** and **1-60** were so far not reported.

2. Objectives

This work provides a significant contribution concerning both the development of useful synthetic methodologies and their application to new total syntheses of three natural products, 15-F_{2t}-IsoP **1-54**, 13,14-dihydro-15-oxo-E_2-IsoP **1-59** and its 8-epimer **1-60**.

Scheme 2.1 Radical α-aminooxygenation and α-amination of carbonyl compounds **2-1**



New methodology for the synthesis of α-hydroxy carbonyl compounds, monoprotected 1,2-diols, protected β-amino alcohols and 1,4-dicarbonyl compounds will be developed based on oxidative reactions of enolates **2-2** generated by deprotonation of carbonyl compounds **2-1** (Scheme 2.1). The generation of α-carbonyl radicals **2-3** from enolates **2-2** by single electron oxidation induced by **1-3** will be central. The feasibility of heterocouplings of **2-3** with persistent radicals, their homocouplings, and radical cyclisations in the presence of persistent radicals will be explored.

Radical α-heterofunctionalisation of carbonyl compounds **2-1** will be studied as follows:

A) α-Aminooxygenation by coupling of **2-3** with the persistent radical TEMPO **1-2** will afford compounds of type **2-4**. This reaction should become a general method for the synthesis of α-aminoxy carbonyl compounds.

B) α-Aminooxygenation of α,β-unsaturated carbonyl compounds will be investigated to learn about the regioselectivity of radical coupling providing α-aminooxygenation products **2-5** and/or γ-aminoxy derivatives **2-6**.

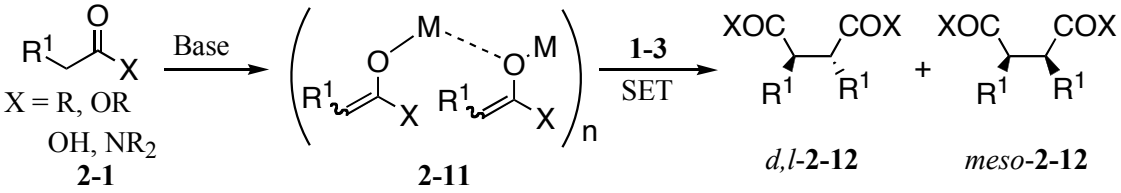
C) Compounds of type **2-4** can be seen as protected alcohols. Scope and limitations of reductive deprotection to α-hydroxy carbonyl compounds **2-7** will be studied.

D) Direct oxygenation of enolates **2-2** or α-carbonyl radicals **2-3** with O_2 will be investigated.

E) Reductions of α-aminoxy carbonyl compounds **2-4** by hydride reagents should enable the access to monoprotected diols **2-8**.

F) New radical amination reactions, such as heterocoupling reactions of α-carbonyl radical **2-3** with nitrogen-centred persistent radicals like 1,3,5-verdazyl **2-9**, will be explored. Moreover the reactivity of **2-9** towards organometallic compounds will be studied.

Scheme 2.2 Oxidative dimerisations of carbonyl compounds **2-1**



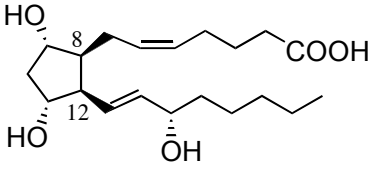
α-Carbonyl radicals **2-3** can also undergo homocoupling reactions giving a direct access to 1,4-dicarbonyl compounds *d,l*-**2-12** and/or *meso*-**2-12** (Scheme 2.2). Since dimerisation reactions reported so far were applied only to a few types of substrates and lack generality, it is necessary to develop new, efficient and widely applicable methodologies, which facilitate access to 1,4-dicarbonyl compounds **2-12** from a large number of precursors containing a carbonyl group. There is a wide field of exploration for different classes of carbonyl derivatives. Not only the scope, but also the mechanism deserves detailed investigations.

Since aggregates **2-11** and the enolate geometry should influence the course of the dimerisation, mechanistic studies should reveal whether the reactions occur by radical addition or homocoupling pathways. The insights gained should be utilised to achieve diastereoselective dimerisations without attaching chiral or bulky auxiliary groups.

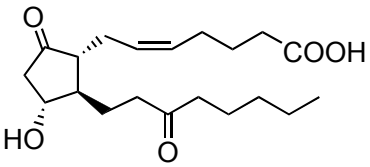
*Total syntheses of 15-F_{2t}-isoprostane **1-54** and 13,14-dihydro-15-oxo-E_2-isoprostane **1-59***

From the multitude of existing isoprostanes, 15-F_{2t}-isoprostane **1-54** is the isomer most often synthesised and biologically most thoroughly studied. The development of a new synthetic strategy, which is shorter, more efficient and also applicable to other isoprostanes would be useful for further biological investigations. By virtue of its stability 15-F_{2t}-IsoP **1-54** is a basic target for testing new methodology.

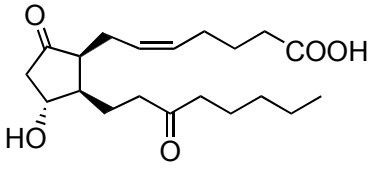
Figure 2.1 IsoP target molecules **1-54**, **1-59** and **1-60**



15-F_{2t}-IsoP **1-54**



13,14-Dihydro-15-oxo-PG E_2 **1-60**



13,14-Dihydro-15-oxo-E_2-IsoP **1-59**

In contrast, the metabolism of most isoprostanes except F_2-IsoP is unknown. This applies also to 15-E_2-IsoP **1-55**. The metabolism of PGE_2 is in the first step an oxidation of the hydroxy group in 15-position to an enone, and the second step is the reduction of the 13,14-double bond to a single bond. Assuming that E_2-IsoP undergoes possibly similar processes, derivative **1-59** and **1-60** maybe important metabolites and their preparation will help to identify its key secondary metabolites and allow the study of their biological activities. Since nature is offering only minute amounts, there is a great need to find ways to produce reference compounds.

The objective of this work is the development of new, short and efficient total syntheses of 15-F_{2t}-IsoP **1-54** and of 13,14-dihydro-15-oxo-E_2-IsoP **1-59**, and respectively 13,14-dihydro-15-oxo-PG E_2 **1-60**. The investigations will concentrate on diastereoselective syntheses, since the natural products are racemic. However, studies on the synthesis of asymmetric cyclisation precursors will also be performed. The IsoP (*8,12-cis*-) and PG (*8,12-trans*-) cyclopentane cores should be synthesised by a biomimetic radical cyclisation. The control of diastereoselectivity in the radical cyclisation must be accurately investigated. The total synthesis aims at high modularity to facilitate the adjustment of the desired substitution pattern of the ring and side chains. The synthetic steps and their order need to be optimised to achieve short and efficient syntheses. This total synthesis is intended as a blueprint, which can be used later for the synthesis of other IsoP, PG, phyto- or neuroprostanes.

3. Oxidative hetero- and homocoupling reactions of enolates: A new method for the synthesis of α-hydroxy carbonyl compounds, 1,2-diols, β-amino alcohols, derivatives of unnatural α-amino acids and 1,4-dicarbonyl compounds

3.1 α-Oxygenations of carbonyl compounds by free radical TEMPO

3.1.1 α-Oxygenation of esters

Linear ethyl pentanoate **3-1a** was chosen for a more detailed investigation of the competing coupling of radicals **2-3** with **1-2** versus homocoupling leading to dimers **2-12** (cf. Schemes 2.1, 2.2).

Scheme 3.1 α-Oxygenation of esters **3-1a-c**

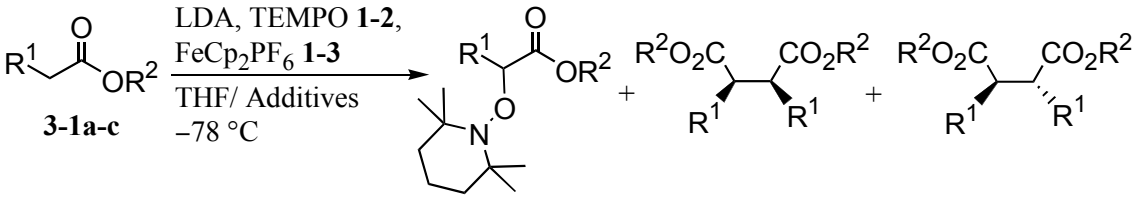
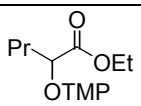
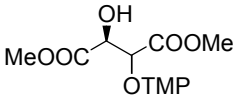
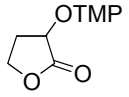


Table 3.1 α-Oxygenation of esters

Entry	Substrate	Product	LDA (equiv.)	Additive (equiv.)	**3-2** (%)	**3-3** (%) (*meso/d,l*)
1	**3-1a**		1.3	HMPA (6)	**3-2a** 64	20 (1:1.5)
2	**3-1a**		1.3	LiCl (6)	**3-2a** 87	4 (1:0)
3	**3-1b**[a]		2.3	LiCl (4.7)	**3-2b** 77[b]	-
4	**3-1b**		2.15	HMPA (6)	**3-2b** 66[c]	-
5	**3-1b**		2.15	-	**3-2b** 65[d]	-
6	**3-1b**		2.5	-	**3-2b** 94[e]	-
7	**3-1c**		1.3	LiCl (6)	**3-2c** 75	-

a) Deprotonation with 2.3 equiv. LDA. b) *syn:anti* 1:1.4. c) *syn:anti* 1:2; d) *syn:anti* 1:1.8. e) Deprotonation 1 h at –78 - –50 °C. *syn:anti* 1:2.2.

Deprotonation of **3-1a** with LDA, followed by oxidation with **1-3** and trapping with **1-2** in the presence of 6 equivalents of HMPA gave **3-2a** in 64% yield (Scheme 3.1, Table 3.1, entry 1). Dimer **3-3a** formed in 20% yield with a 1:1.5 *meso:d,l* diastereoselectivity. In

contrast, the α-oxygenation was very efficient in the presence of LiCl giving **3-2a** in 87% yield and only 4% of *meso*-**3-3a** (entry 2). The α-oxygenation of ester **3-1b** with a chiral centre in β-position occurred also efficiently in 65-77% yields (entries 3-5). Dimer formation was not observed. Product **3-2b** was isolated in excellent yields of 94%, when a somewhat larger excess of LDA was used and the deprotonation was performed for longer time (entry 6). The α-oxygenation of **3-1b** proceeded with low diastereoselectivity. The configuration of the *syn*- and *anti*-diastereomers was assigned by comparison of the NMR data with those of the derived known tartrates (*vide infra*). Butyrolactone **3-1c** gave the trapping product **3-2c** in 75% yield (entry 7). No dimer **3-3c** was detected.

Table 3.2 Significant NMR data of compounds **3-2a-c**

	3-2a	*syn*-**3-2b**	*anti*-**3-2b**	**3-2c**
	δ (ppm), multiplicity			
C*H*ON	4.14, dd	4.65, s	4.81, s	4.71, dd
*C*HON	85.5, d	83.6, d	85.8, d	80.3 d

The structural assignment of **3-2a-c** is based on their NMR data (Table 3.2). The α-proton absorbs at 4.14-4.81 ppm in the ^{1}H NMR spectra. The α-carbon appears as a doublet at 80.3-85.8 ppm in the ^{13}C NMR spectra.

3.1.2 α-Oxygenation of nitriles and amides

Nitriles and amides proved to be suitable substrates for α-oxygenation with TEMPO **1-2** (Scheme 3.2, Table 3.3). Phenylacetonitrile **3-4a**, octonitrile **3-4b** and 3-methyl-3-hydroxy butyronitrile **3-4c** formed the corresponding α-(tetramethylpiperidinyloxy)nitriles **3-5a-c** in high yields (entries 1-5). The additive LiCl had no influence on the efficiency (entries 1, 3 versus 2, 4, 5). Generally, dimerisation did not take place. The linear tertiary amides **3-4d** and **3-4e** underwent α-oxygenation with TEMPO in high yields in the presence or absence of LiCl (entries 6, 7). In some experiments, besides **3-4d** small amounts (maximal 5%) of the dimer of **3-4d** were isolated. Branched amides like *N,N*-dimethylisobutyramide **3-4f** or *N,N*-diisopropylisobutyramide **3-4g** are hindered at the α-carbonyl position. The α-carbonyl radical was probably generated since **1-3** was consumed while it was added to the enolate solution, indicating oxidation of the enolate. Nonetheless, **3-4f** gave the α-(tetramethylpiperidinyloxy)amide **3-5f** in low 5-13% yield (entries 8, 9), while the more sterically hindered **3-4g** did not react at all and the substrate was recovered in 70% yield.

N,N,N',N'-tetramethylglutardiamide **3-4h** was subjected to twofold deprotonation and oxidation/trapping with TEMPO **1-2** under similar conditions. Product **3-5h** was isolated in low yields (entries 11, 12). The diastereoselectivity amounted to a 4:1 *d,l/meso* ratio. The isomer *meso*-**3-5h** has a plane of symmetry, which is reflected in its NMR spectra and allowed the assignment of the diastereomers.

Scheme 3.2 α-Oxygenation of amides and nitriles

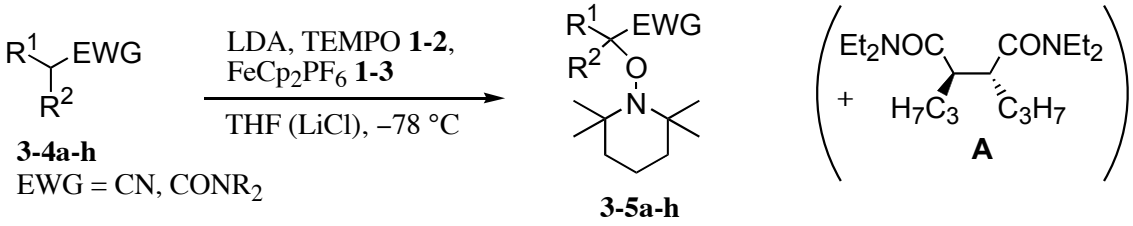
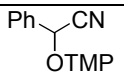
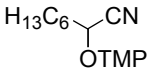
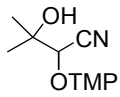
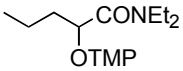
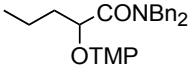
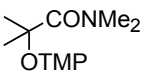
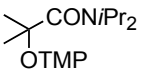
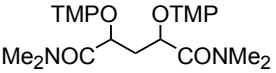


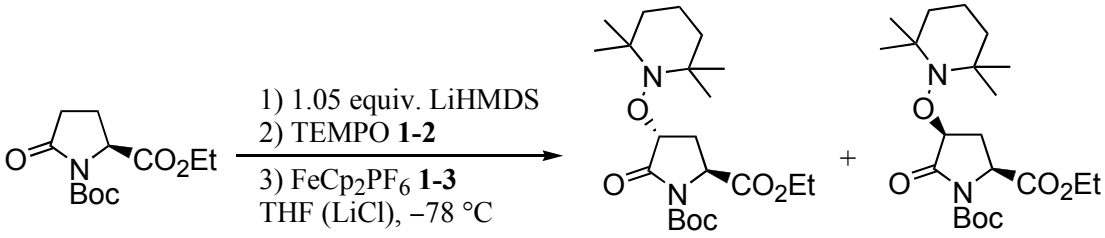
Table 3.3 α-Oxygenation of amides and nitriles

Entry	Substrate	Product **3-5a-h**	LiCl (equiv.)	**3-5** (%)
1	**3-4a**		-	**3-5a** 93
2			4.7	**3-5a** 73
3	**3-4b**		-	**3-5b** 78
4			4.7	**3-5b** 92
5[a]	**3-4c**		6	**3-5c** 99
6[b]	**3-4d**		-	**3-5d** 94
7	**3-4e**		6	**3-5e** 74
8[c]	**3-4f**		4.7	**3-5f** 5
9			-	**3-5f** 13
10[d]	**3-4g**		6	-
11[e,f]	**3-4h**		4.7	**3-5h** 34
12[e,f]			6	**3-5h** 28

a) Deprotonation with 2.3 equiv. LDA at –78 - –50 °C for 35 min. b) In some experiments small amounts (maximum 5%) of the dimer **A** were isolated. c) Deprotonation time 1 h 15 min. A very polar material, not assignable, which contained an isobutyramide unit, was the major product. d) **3-4g** was recovered in 70% yield. e) Double deprotonation with 2.3 equiv. LDA at –78 - –65 °C for 0.5 h. f) *d,l/meso* 4:1.

Optically pure *N*-Boc-pyroglutamate **3-4i** was an interesting substrate whose stereocentre may induce a diastereoselective α-oxygenation (Scheme 3.3). An important issue was the retention of configuration at the chiral centre without loss of enantiopurity.[99] In earlier experiments,[25] deprotonation of **3-4i** with 1.3 equivalents of LiHMDS followed by oxidation with **1-3** in the presence of **1-2** gave *(2S,4R)*-**3-5i** with 78% ee and *(2S,4S)*-**3-5i** with 81% ee in 61% combined yield as a separable 1:1.5 diastereomeric mixture. To improve this result, the amount of base was reduced. Experiments with 1.05 equivalents of LiHMDS furnished *(2S,4R)*-**3-5i** and *(2S,4S)*-**3-5i** in 70% yield with a 1:1.2 diastereomeric ratio. The products were enantiopure as shown by HPLC measurements using a chiral DAICEL-OD column.

Scheme 3.3 Oxygenation of Boc-protected ethyl *(S)*-2-pyrrolidone-5-carboxylate



3-4i *(2S,4R)*-**3-5i** *(2S,4S)*-**3-5i**

70% 1:1.2

Table 3.4 Significant NMR data of α-(tetramethylpiperidinyloxy) nitriles **3-5a-c**

	3-5a	**3-5b**	**3-5c**
	δ (ppm), multiplicity		
C*H*ON	5.50, s	4.52, dd	4.59, s
*C*HON	76.7, d	74.3, d	80.0, d

In compounds **3-5a-c** the carbon atom bearing the TMP-group displays a doublet at 74.3-80.0 ppm (Table 3.4). The corresponding proton gives a singlet at 5.50 and 4.59 ppm in **3-5a** and **3-5c**, respectively. In **3-5b** the same proton gives a dd at 4.52 ppm.

Table 3.5 Significant NMR data of products **3-5d-i**

	3-5d	**3-5e**	**3-5f**	*d,l*-**3-5h**	*meso*-**3-5h**	(*2S,4R*)-**3-5i**	(*2S,4S*)-**3-5i**
	δ (ppm), multiplicity						
C*H*ON	4.41, dd	4.59, m	-	4.72, dd	4.32, dd	4.69, dd	4.55, dd
*C*HON	81.3, d	81.4, d	83.5, d	79.3, d	79.1, d	81.4, d	81.9, d

The characteristic signals of the carbon atom bearing the TMP-group are presented in Table 3.5, together with the corresponding proton resonance.

3.1.3 α-Oxygenation of acid 3-6

The double deprotonation of heptanoic acid **3-6** with 2.5 equivalents of LDA generated the enediolate, which was subsequently oxidised and trapped by **1-2** (Scheme 3.4, Table 3.6, entry 1). Product **3-7** was obtained in a low yield of 33%. It was accompanied by 27% of dimer **3-8** as a 1:1 diastereomeric mixture, 6% of disproportionation product **3-9** and 25% of unchanged substrate **3-6**. The yield did not improve, when the carboxylic acid was deprotonated by 1.5 equivalents LDA followed by addition of another equivalent of BuLi. Oxygenation product **3-7** was isolated in 37% yield. Dimer **3-8** was not detected, but the overall mass balance was low (entry 2). Experiments in the presence of additives as well as longer deprotonation time at higher temperature gave similar results (entries 3, 4). The α-oxygenation of the enediolate generated by deprotonation with $LiNEt_2$[100] proved to be more efficient affording product **3-7** in an improved 51% yield (entry 5). Formation of dimer **3-8** and disproportionation product **3-9** could not be further suppressed.

Scheme 3.4 α-Oxygenation of heptanoic acid **3-6**

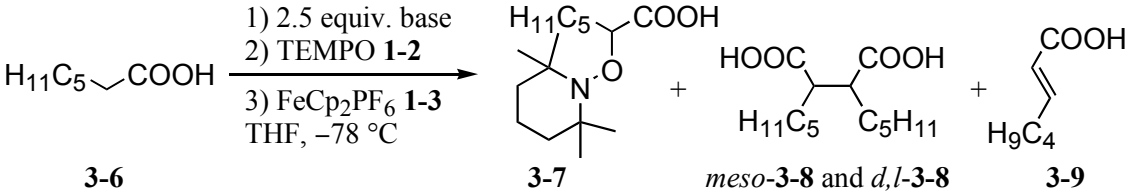


Table 3.6 Conditions of α-oxygenation of heptanoic acid **3-6**

Entry	Base (equiv.)[a]	Additives (equiv.)	**3-7**	**3-8** (*meso/d,l*)	**3-9**	**3-6**
1	LDA (2.5)	-	33	27 (1:1)	6	25
2	LDA (1.5) BuLi (1.0)	-	37	-	trace	trace
3	LDA (2.5)	LiCl (4.7) HMPA (6)	38	17 (1:1)	8	19
4[b]	LDA (2.5)	LiCl (4.7)	32	7 (1:0)	4	8
5[c]	$LiNEt_2$ (2.5)	LiCl (4.7)	51	14 (1:0)	9	22
6[b]	$LiNEt_2$ (2.5)	LiCl (4.7)	33	7 (1:0)	6	13
7	$LiNEt_2$ (2.5)	LiCl (4.7) HMPA (6)	24 (impure)	-	trace	trace

a) If not specified, the deprotonation was performed at −78 - −35 °C for 1 h. b) Deprotonation at −78 °C for 10 min, then at r.t. for 2.5 h. c) Deprotonation for 10 min at −78 °C, then at 0 °C for 1 h.

Longer deprotonation time at higher temperature had a negative influence on the efficiency of the oxygenation (entry 6), while the use of HMPA as an additive led to the formation of complex mixtures (entry 7).

3.1.4 α-Oxygenation of ketones

Various ketones were investigated in α-oxygenation reactions with TEMPO **1-2** (Scheme 3.5). Aromatic ketones behaved similarly as esters. Dimers **3-12** were formed to a rather large extent in competition to desired **3-11** (Table 3.7). Propiophenone **3-10a** yielded **3-11a** in only 30% yield (entry 1). Major product was dimer **3-12a**, which was isolated in 59% yield with a high 10.5:1 *d,l/meso* diastereoselectivity. The competing dimerisation was very unusual in the presence of excess **1-2.** The cross-coupling of **2-3** with radical **1-2** should prevail (cf. Scheme 2.1).[46] The high diastereoselectivity of the formation of dimers **3-12a** was very surprising. The selectivity for formation of **3-11a** improved to 52% yield in the presence of HMPA (entry 2). Nonetheless dimerisation occurred in 47% yield. The *d,l/meso* ratio of 6:1 was however lower. When LiCl was used as additive, α-oxygenation product **3-11a** was obtained in 78% yield (entry 3), while dimer **3-12a** was isolated in 21% yield with a 5:1 *d,l/meso* ratio. The same pattern was observed for butyrophenone **3-10b**, which afforded **3-11b** in 38% yield in the absence of additives (entry 4). Dimer **3-12b** was isolated in 55% yield with a 45:1 *d,l/meso* ratio. In the presence of LiCl, the oxygenated product **3-11b** and dimer *d,l*-**3-12b** were isolated in 70% and 30% yield, respectively (entry 5). The α-oxygenated product **3-11c** resulting from isobutyrophenone **3-10c** was obtained in low yield probably due to steric hindrance, similar to isobutyramides **3-4f** or **3-4g** (entry 6). The oxygenation method is on the other hand well suited for aliphatic acyclic and cyclic ketones, which gave oxygenated products **3-11d-3-11g** in high yields (entries 7-12). LiCl did not modify the reaction course significantly. Dimers **3-12** were rarely isolated and if so only in small amounts (entry 9).

Scheme 3.5 α-Oxygenation of ketones

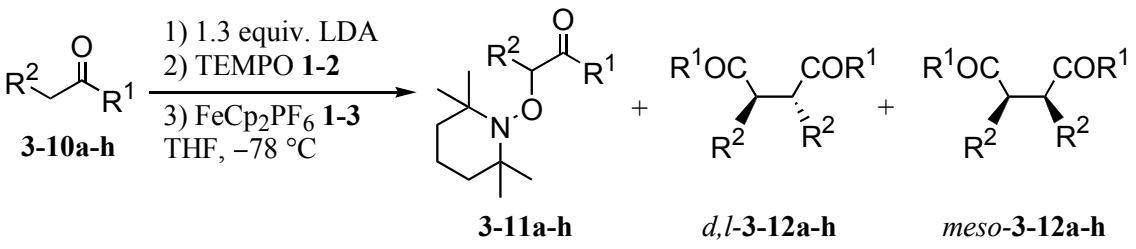
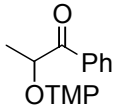
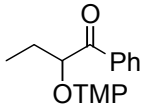
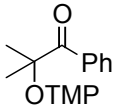
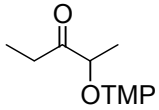
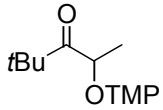
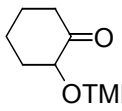
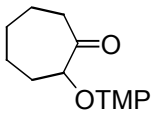
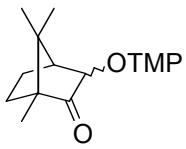


Table 3.7 α-Oxygenation of ketones **3-10**

Entry	Substrate	Product	Additive (equiv.)	**3-11a-h** (%)	**3-12a-h** (%) (*d,l/meso*)
1	**3-10a**		-	**3-11a** 30	**3-12a** 59 (10.5:1)
2			HMPA (6)	**3-11a** 52	**3-12a** 47 (6:1)
3			LiCl (4.7)	**3-11a** 78	**3-12a** 21 (5:1)
4	**3-10b**		-	**3-11b** 38	**3-12b** 55 (45:1)
5			LiCl (4.7)	**3-11b** 70	**3-12b** 30 (1:0)
6[a]	**3-10c**		-	**3-11c** 18	-
7	**3-10d**		-	**3-11d** 79	-
8	**3-10e**		-	**3-11e** 94	-
9	**3-10f**		-	**3-11f** 85	**3-12f** 9 (1:2.5)
10			LiCl (4.7)	**3-11f** 77	-
11			HMPA (6)	**3-11f** 49	
12	**3-10g**		LiCl (4.7)	**3-11g** 87	-
13	**3-10h**		-	**3-11h** 85[b]	**3-12h** 2 *(exo,exo)*
14			LiCl (4.7)	**3-11h** 95[c]	-

a) 62% of substrate was recovered. b) *exo/endo* 1:1.1. c) *exo/endo* 1.1:1.

The α-oxygenation of chiral *(R)*-camphor **3-10h** proceeded in high yields (entries 13, 14). Surprisingly and in contrast to polar oxygenations,[101] oxygenation by TEMPO occurred from both of the radical faces yielding diastereomers *exo*-**3-11h** and *endo*-**3-11h** in a 1:1 ratio. The yields were also excellent in the presence of LiCl (entry 14).

Aliphatic linear unsymmetrical ketones **3-10i-k** were an interesting substrate class, since both α-carbonyl positions can be deprotonated and subsequently oxygenated (Scheme 3.6). Deprotonation of cyclopropyl methyl ketone **3-10i** for 20 minutes followed by oxidation in the presence of TEMPO **1-2** gave only 4% of pure TEMPO trapping product **3-11i** with complete regioselectivity (Table 3.8, entry 1). Oxygenated **3-13i** formed by an aldol addition

of the TEMPO adduct **3-11i** with unreacted enolate of **3-10i**. The major product was **3-13i** isolated in 50% yield. Dimers **3-12i** and **3-12'i** were isolated in 20% and 22% yield, respectively. The product distribution changed when the deprotonation time was reduced to 10 minutes and LiCl was used as an additive (entry 2). The yields of products **3-11i** and **3-13i** improved to 23% and 68% respectively. Only small amounts of dimers **3-12i** and **3-12'i** were detected.

Scheme 3.6 α-Oxygenation of methyl ketones

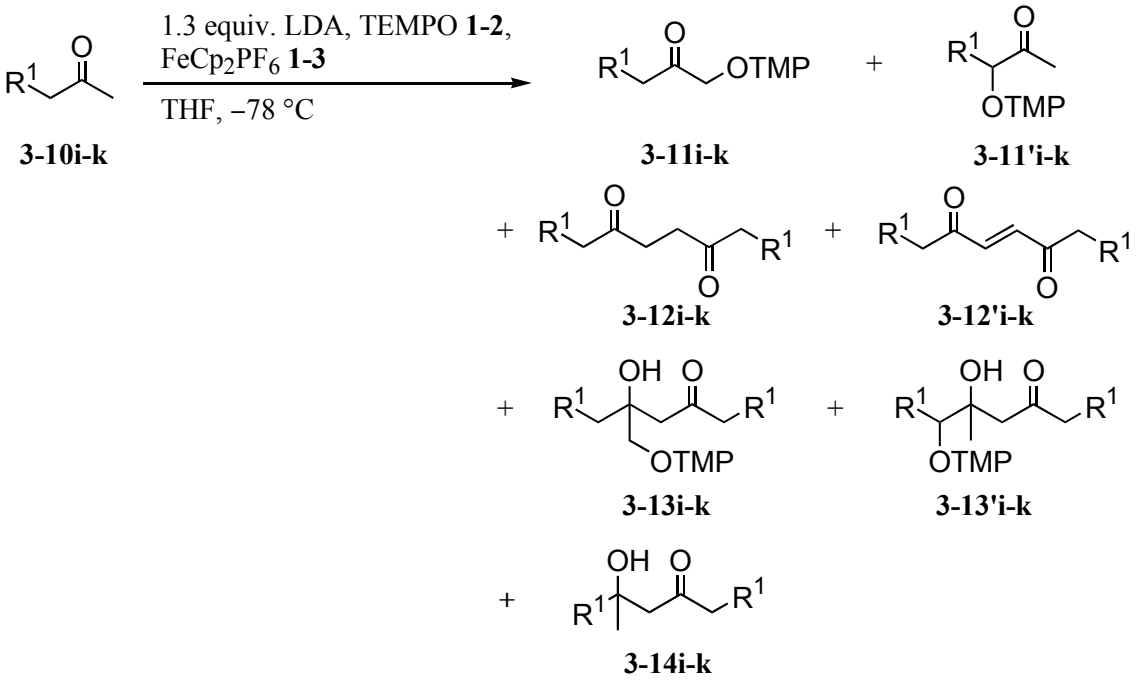
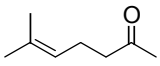
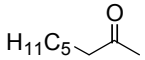


Table 3.8 α-Oxygenation of unsymmetrical ketones **3-10i-k**

Entry	Substrate	Additive (equiv.)	**3-11+3-11'** (%)	**3-12+3-12'** (%)	**3-13 (+3-13')** (%)	**3-14** (%)
1[a]	 **3-10i**	-	4 (1:0)	42 (1:1)	50	-
2[b]		LiCl (6)	23 (1:0)	traces	68	-
3[c]	 **3-10j**	-	16 (1.9:1)	14[d] (1.3:1)	26 (+traces)	-
4[c]		LiCl (6)	43 (7.4:1)	-	19 (+traces)	9
5[c]	 **3-10k**	LiCl (6)	29 (12:1)	-	30 (+traces)	-
6[e]		LiCl (6)	37 (8.8:1)	traces	24 (+traces)	14

a) Deprotonation 20 min. b) Deprotonation 10 min. c) Deprotonation 5 min. d) Product **3-12'j** was isolated as an inseparable mixture with a not assignable dimer, which contained the unit tetramethylpiperidinyloxy. e) Deprotonation 30 min.

For 6-methyl-5-hepten-2-one **3-10j** deprotonation was performed for 5 minutes in the presence or absence of LiCl (Table 3.8, entries 3 and 4). In the absence of LiCl, α-oxygenated products **3-11j** and **3-11'j** were obtained in 16% with a low terminal versus internal selectivity of 1.9:1. The oxidation/TEMPO trapping/aldol addition product **3-13j** was isolated in 26% yield, while products **3-12** and **3-12'** were also formed in 14% yield. In the presence of LiCl, the yield of **3-11j** and **3-11'j** improved to 43%, and the selectivity for the formation of **3-11j** to 7.4:1 (entry 4). Product **3-13j** was isolated in 19% yield, while aldol product **3-14j** was formed in 9% yield. The enolate of 2-octanone **3-10k** was oxidised in the presence of LiCl, testing short and long deprotonation times of 5 and 30 minutes, respectively (entries 5 and 6). Products **3-11k** and **3-11'k** were obtained in low to moderate yields of 29% and 37%, respectively, with high regioselectivities of 12:1 and 8.8:1. Compound **3-13k** was formed in 30 and 24% yields. Products **3-14k** and **3-12'k** were also detected. The low yields of targeted **3-11** were due to a multitude of competing reactions leading to formation of byproducts **3-12**, **3-13** and **3-14**. Their formation was suppressed partially by the presence of LiCl, which affected the outcome of these experiments positively.

Table 3.9 Significant NMR data of compounds **3-11i-y** and **3-13i-y**

	3-11i	**3-11j**	**3-11k**	**3-13i**	**3-13j**	**3-13k**
	δ (ppm), multiplicity					
C*H*$_2$ON	4.51, s	4.38, s	4.39, s	3.73, 3.79[a]	3.75[a]	3.74[a]
*C*H$_2$ON	83.4, t	83.1, t	83.0, t	81.8, t	80.8, t	81.2, t

a) AB system.

The structures of compounds **3-11i-k** and **3-13i-k** were unambiguously assigned by ^{1}H and ^{13}C NMR spectroscopy. The most characteristic signals are those of the methylene group bearing the TMP-group (Table 3.9).

Key results:

1. The synthesis of α-tetramethylpiperidinyloxy carbonyl compounds can be efficiently accomplished via deprotonation/oxidation with ferrocenium hexafluorophosphate **1-3**/coupling of the resulting α-carbonyl radical by TEMPO **1-2** in high yields for substrates which are not hindered at the α-position. α-Branched carbonyl compounds **3-4f**, **3-4g**, **3-10c** underwent this reaction in poor yields.

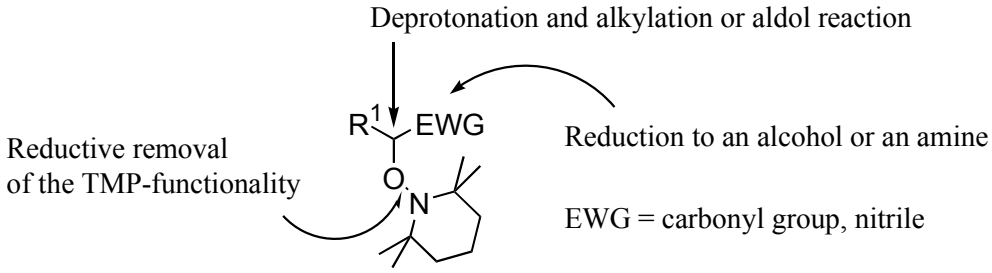
2. Oxidative dimerisation competed with the α-oxygenation for aromatic esters and ketones, whose enolates aggregate strongly in solution. The yields were considerably improved by using LiCl as an additive.

3. Aliphatic unsymmetrical methyl ketones **3-10** having two enolisable α-positions gave the α-oxygenated products in low to moderate yields, but good regioselectivity since compounds **3-11'** and **3-13'** were formed in low yields. Competing oxidative dimerisations and aldol additions limited the yields leading to the formation of products **3-12**-**3-14**. The presence of LiCl suppressed the formation of products **3-12** and improved the overall mass balance.

3.2. Reactions of α-tetramethylpiperidinyloxy carbonyl compounds and nitriles

α-Tetramethylpiperidinyloxy carbonyl compounds and nitriles **3-2**, **3-5**, **3-7** and **3-11** can be considered protected α-hydroxy carbonyl compounds. The carbonyl function may be reduced to an alcohol, the N-O bond can be reductively cleaved to liberate the hydroxy group and the α-hydrogen to the carbonyl could be deprotonated giving an enolate, which may undergo anionic reactions. Similar reactivity can be envisaged for α-tetramethylpiperidinyloxy nitriles.

Figure 3.1 Possible reactions of compounds of type **3-2**, **3-5**, **3-7** and **3-11**

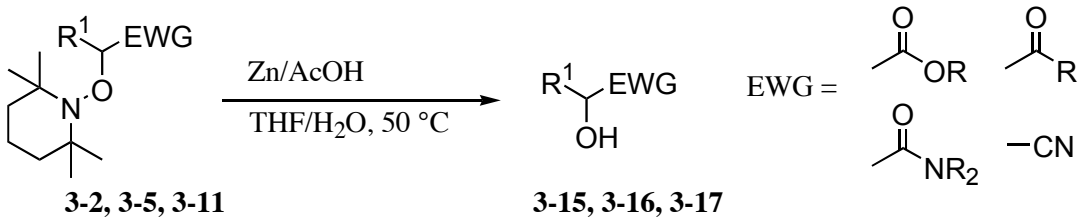


3.2.1. Synthesis of α-hydroxy carbonyl compounds via reductive deprotection of the tetramethylpiperidine functionality

The 2,2,6,6-tetramethylpiperidine functionality of α-TMPoxy esters **3-2** was previously removed reductively by treatment with Zn/AcOH in THF/H_2O affording α-hydroxy esters **3-15**.[10a, 26a,b] This method was now optimised for a large number of substrates such as α-TMPoxy ketones, esters, nitriles, lactones and amides (Scheme 3.7, Table 3.10). Most of the reactions provided α-hydroxy carbonyl compounds **3-15**-**3-17** in high yields

(entries 1, 3-7). The procedure was also adapted for the synthesis of the water-soluble hydroxy butyrolactone **3-15c**, which was obtained in a moderate 54% yield (entry 2).

Scheme 3.7 Reductive deprotection of the TMP functionality



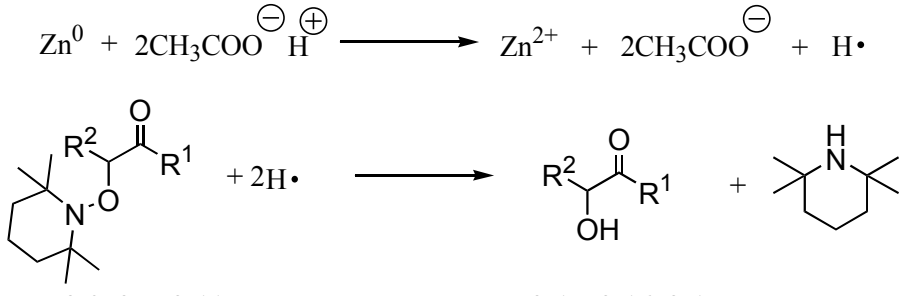
3-2, 3-5, 3-11 **3-15, 3-16, 3-17**

Table 3.10 Yields and significant NMR data of α-hydroxy carbonyl derivatives

Entry	Substrate (mmol)	Method	Product	Yield (%)	δ (ppm), multiplicity	
					C*H*OH	*C*HOH
1	**3-2b**	A	**3-15b**	75	4.68, s[a]	73.1, d[a]
					4.62, s[b]	72.3, d[b]
2	**3-2c**	D	**3-15c**	54	4.50, dd	67.3, d
3	**3-5b**	C	**3-16b**	94	4.47, t	61.2, d
4	**3-5d**	A	**3-16d**	83	4.35, m	67.8, d
5	**3-11e**	B’	**3-17e**	71	4.57, q	68.4, d
		B		55		
6	**3-11f**	B	**3-17f**	90	4.08, dd	75.3, d
7	**3-11h**	A	**3-17h**	71	*exo* 3.72, s	76.9, d
	3-11h[c]	C	**3-17h**	87	*endo* 4.18, d	74.1, d

a) *(2S,3R)*-isomer. b) *(2S,3S)*-isomer. c) 0.55 mmol **3-11h** were heated with 1.35 g Zn (38 equiv.) and 3 mL AcOH (95 equiv.) in 4 mL THF/H_2O 1:1 at 50 °C for 1.5 h. The reaction was not complete by TLC, thus another 1.3 g Zn and 3 mL AcOH were added and heating was continued for 1 h.

Scheme 3.8 Mechanism of reduction with Zn/AcOH

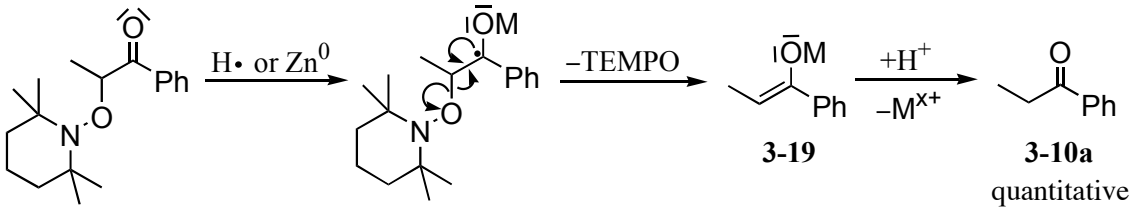


3-2, 3-5, 3-11 **3-15, 3-16, 3-17**

A possible mechanism for the reduction consists of oxidation of Zn^0 by acetic acid to produce hydrogen atoms. The O-N bond is reduced by 2 hydrogen atoms, and the desired α-hydroxy carbonyl compounds **3-15**, **3-16** and **3-17** and 2,2,6,6-tetramethylpiperidine are formed.

However, a different course was observed with α-TEMPOxy propiophenone **3-11a** (Scheme 3.9). Here the carbonyl oxygen was more easily attacked by the electron poor hydrogen atom because of the lower reduction potential of the aromatic carbonyl group and a ketyl radical **3-18** is formed (Scheme 3.9).[102] Alternatively, also protonation of the Lewis-basic carbonyl oxygen is viable, which increases the electron-accepting power of the carbonyl group. Direct reduction by Zn^0 gives the same ketyl radical. Subsequent β-fragmentation of TEMPO leads to the Zn enolate of propiophenone **3-19**, which is hydrolysed to **3-10a**.

Scheme 3.9 Mechanism of reduction of propiophenone **3-11a**



3-11a **3-18** M = H, Zn **3-19** **3-10a** quantitative

Optimisation experiments were performed in order to reduce the large excess (40 equiv.) of zinc and replace acetic acid (Table 3.11). Amide **3-5d** was reduced to **3-16d** in low yields in the presence of 3.5 equiv. Zn and 8.7 equiv. HCl (entry 1). The reduction of **3-5d** with 20 equiv. Zn and 50 equiv. AcOH gave the α-hydroxy amide **3-16d** in 44% yield (entry 2). The reagent excess described in the original procedure seems to be necessary for achieving good yields. (*R*)-Camphor derivative **3-11h** was recovered quantitatively when it was heated with 12 equivalents Zn and 30 equivalents HCl (entry 3). Thus, the replacement of acetic acid by the easier removable HCl and reduction of the amount of Zn dust are not tolerated.

Table 3.11 Optimisation experiments of reductive deprotection

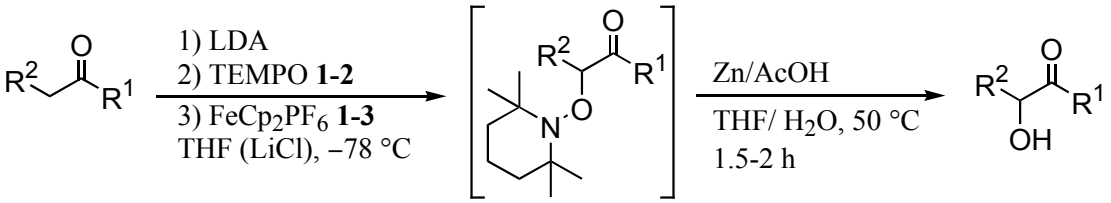
Entry	Substrate	Conditions	Product	Yield (%)
1[a]	**3-5d**	3.5 equiv. Zn/ 8.7 equiv. HCl	**3-16d**	37
2	**3-5d**	20 equiv. Zn/ 50 equiv. AcOH	**3-16d**	44
3[b]	**3-11h**	12 equiv. Zn/ 30 equiv. HCl	**3-17h**	0

a) 21% **3-5d** was recovered. b) Substrate **3-11h** was recovered.

Synthesis of α-hydroxy carbonyl compounds from carbonyl compounds in one pot

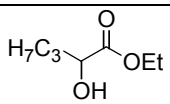
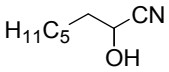
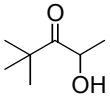
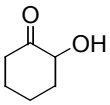
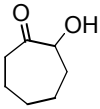
The combination of enolate aminoxylation and the reductive cleavage of the TMP-functionality to a one-pot 2 step process is attractive for the more direct preparation of α-hydroxy carbonyl compounds (Scheme 3.10). The α-tetramethylpiperidinyloxy carbonyl compounds **3-2**, **3-5** and **3-11** were synthesised as described before, but the crude product containing ferrocene and some TEMPO was immediately treated with Zn/AcOH in THF/H_2O at 50 °C. Conditions needed to be adjusted partly by increasing the solvent or reagent amount (Table 3.12). Ethyl valerate **3-1a** yielded product **3-15a** efficiently (entry 1).

Scheme 3.10 Synthesis of α-hydroxy carbonyl compound **3-15**, **3-16**, and **3-17** in one pot



3-1, 3-4, 3-10 **3-2, 3-5, 3-11** **3-15, 3-16, 3-17**

Table 3.12 Conditions and yields of the one pot hydroxylation

Entry	Substrate[a]	Product	Isolation method	**3-15**, **3-16**, **3-17** (%)
1	**3-1a**		G	**3-15a** 76
2	**3-4b**[b]		C	**3-16b** 85
3	**3-4b**[c]		C	**3-16b** 54
4	**3-10c**		B’	**3-17c** 31
5	**3-10f**		B	**3-17f** 46
6	**3-10g**[d]		B	**3-17g** 59
7	**3-10g**		B	**3-17g** 38

a) Unless otherwise noted scale 2 mmol, 0.25*M* in THF/H_2O 1:1, 5.2 g Zn, 12 mL AcOH. b) After 1.5 h 25 equiv. AcOH and 11 equiv. Zn were added. c) Scale 15 mmol; 0.071*M* in THF/H_2O 3:1. The product contained traces of heptanol. d) 50 equiv. Zn.

Octonitrile **3-4b** afforded product **3-16b** in high yields on a 2 mmol scale (entry 2) and in moderate yields on a 15 mmol scale (entry 3). For smaller molecules the efficiency decreased, α-hydroxy *tert*-butyl ethyl ketone **3-17c** and α-hydroxy cyclohexanone **3-17f** were obtained in moderate yields (entries 4 and 5). Cycloheptanone **3-10g** gave 59% of hydroxy ketone **3-17g** with 50 equiv. Zn (entry 6), while the product was isolated in only 38% yield with 40 equiv. Zn (entry 7).

Key results: The reductive deprotection of α-tetramethylpiperidinyloxy carbonyl derivatives to α-hydroxy carbonyl compounds **3-15**, **3-16** and **3-17** was applied for a large number of representative examples. A one pot synthesis of **3-15**, **3-16** and **3-17** works for all investigated substrates, however, this sequence is only in some cases, mostly for small setups and non volatile products, as efficient as the stepwise procedure.

3.2.2. A new efficient access to monoprotected 1,2-diols and O-protected amino alcohols via reduction of α-tetramethylpiperidinyloxy carbonyl compounds with hydride reagents

Typical hydride reagents such as $NaBH_4$ or $LiAlH_4$ reduced the carbonyl functionality selectively in the presence of the α-tetramethylpiperidinyloxy unit (Scheme 3.11, Table 3.13). The reduction of different substrates was tested with respect to the *syn*/*anti*-diastereoselectivity. α-(Tetramethylpiperidinyloxy)propiophenone **3-11a** was reduced to the monoprotected diol **3-20a** in high yields with good *syn:anti* diastereoselectivity of 6.5:1 using $NaBH_4$ (Scheme 3.11, Table 3.13, entry 1). Reduction of α-(tetramethylpiperidinyloxy) butyrophenone **3-11b** occurred also in excellent yields and good to high diastereoselectivities applying both $NaBH_4$ and $LiAlH_4$ (entries 2, 3, and 4).

Scheme 3.11 Reduction of ketones **3-11** with hydride reagents (relative stereochemistry shown)

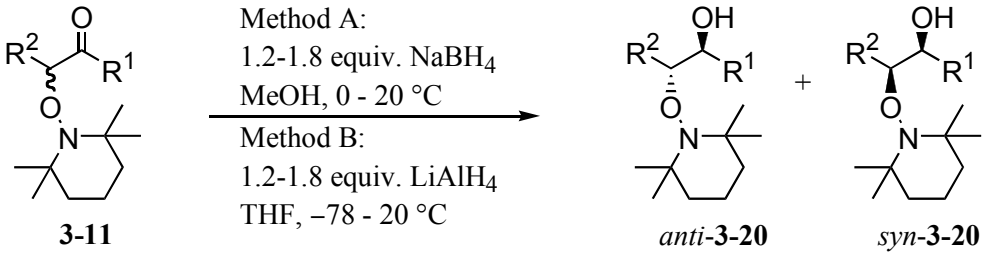
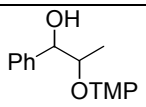
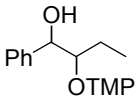
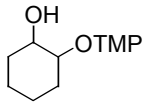
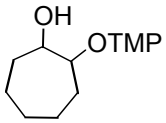
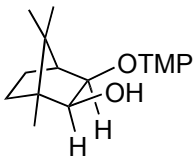
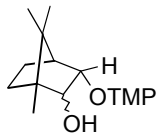


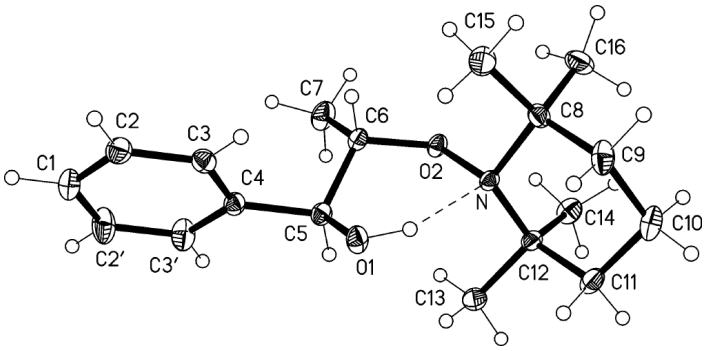
Table 3.13 Reduction of α-tetramethylpiperidinyloxy ketones **3-11**

Entry	Substrate	Method	Product **3-20**	**3-20** (%)	Diastereomeric ratio[a]
1	**3-11a**	A		**3-20a** 89	6.5 :1
2	**3-11b**	A		**3-20b** 95	8:1
3	**3-11b**	A		**3-20b** 99	9.2:1
4	**3-11b**	B		**3-20b** 85	11.2:1
5	**3-11f**	A		**3-20f** 100	2.7:1
6	**3-11f**	B		**3-20f** 90	1:1.1
7	**3-11g**	A		**3-20g** 75	*cis/trans* 4:1
8	**3-11g**	B		**3-20g** 92	*cis/trans* 2.9:1
9	*exo*-**3-11h**[b]	A		**3-20h** 0	-
10	*exo*-**3-11h**	B		**3-20h** 91	4.3:1
11	*exo*-**3-11h**	B		**3-20h** 75	>20:1
12	*endo*-**3-11h**	B		**3-20h** 100	4.6:1

a) *syn:anti* for **3-11a** and **3-11b**. *cis/trans* for **3-11f** and **3-11g**. *2-exo,3-exo:2-endo,3-endo* for *exo*-**3-11h**. *2-endo,3-endo:2-exo,3-endo* for *endo*-**3-11h**. b) 16 equiv. $NaBH_4$, MeOH, 0 °C, 30 min; the impure substrate was recovered.

The unequivocal configuration assignment of *syn*-1-phenyl-2-(tetramethylpiperidinyloxy)-1-propanol *syn*-**3-20a** was accomplished by X-ray crystallography. The compound is arranged in an antiperiplanar conformation of the large phenyl and tetramethylpiperidinyloxy units, which is stabilised by a hydrogen bond between the hydrogen of the hydroxy group and the nitrogen atom of the tetramethylpiperidinyl unit.

Figure 3.2 X-Ray crystal structure of *syn*-1-hydroxy-1-phenyl-2-(tetramethylpiperidinyloxy) propane *syn*-**3-20a**

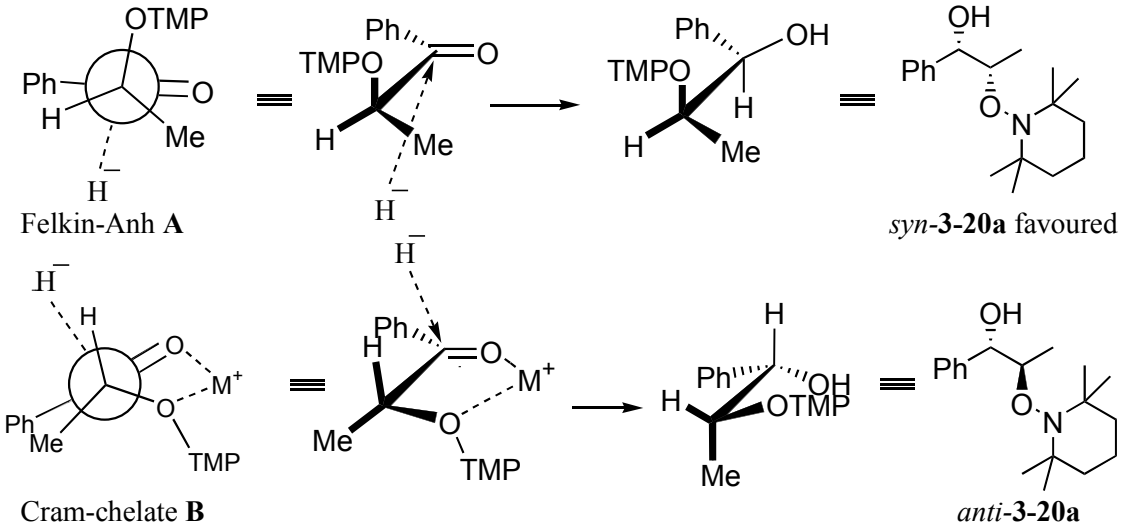


Significant NMR data for the *syn*- and *anti*-isomers of **3-20a** and **3-20b** are presented in the Table 3.14. The assignment of the diastereomers is in agreement with literature known data of 1-phenyl-1,2-dihydroxy propane.[103]

Table 3.14 Chemical shifts of compounds **3-20a,b**

Entry	Isomer	δ (ppm), (m, *J* (Hz))		
		H1/C1	H2/C2	OH
1	*syn*-**3-20a** (major)	4.76 (d, 8.6)/80.9 (d)	4.16 (dq, 8.6, 6.3)/80.8 (d)	1.25 (br. s)
2	*anti*-**3-20a**	5.07 (t, 2.5)/74.8 (d)	4.12 (m, 6.6, 3.2)/82.8 (d)	2.43 (d, 2.6)
3	*syn*-**3-20b** (major)	4.80 (d, 8.8)/79.6 (d)	3.94 (dt, 8.5, 3.1)/84.9 (d)	1.07-1.23 (br.s)
4	*anti*-**3-20b**	5.10 (br s)/73.3 (d)	3.94 (m)/87.5 (d)	2.44 (d, 4.4)

Scheme 3.12 Rationalisation of formation of *syn*- and *anti*-**3-20a** and **3-20b** respectively



Addition of a nucleophile to a carbonyl compound with an electron withdrawing group in the α-position occurs usually with high *syn*-selectivity.[104] Thus a Felkin-Anh transition state **A** explains the selective formation of *syn*-**3-20a** and *syn*-**3-20b** (Scheme 3.12). On the other hand, minor *anti*-**3-20a** and *anti*-**3-20b** maybe formed via a Cram-chelate transition state **B**.

The reduction of 2-tetramethylpiperidinyloxy cyclohexanone **3-11f** with $NaBH_4$ and $LiAlH_4$ afforded monoprotected cyclohexanone-1,2-diol *cis*-**3-20f** and *trans*-**3-20f** in excellent yields (Table 3.11, entries 5 and 6). The *cis/trans* diastereoselectivity amounted to 2.7:1 with $NaBH_4$, while $LiAlH_4$ gave no selectivity. The structurally similar cycloheptanone derivative **3-11g** was reduced in high yields, however, higher *cis/trans* diastereoselectivities of 4:1 with $NaBH_4$ and 2.9:1 with $LiAlH_4$ were found (entries 7 and 8).

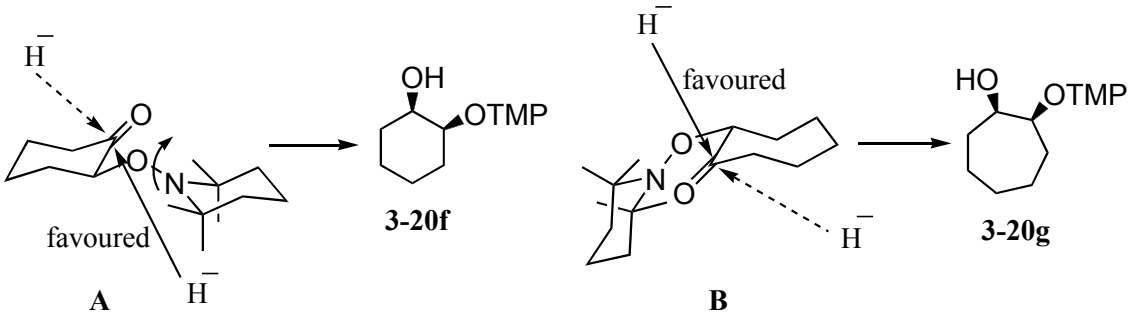
The configuration of the *cis* and *trans* isomers of **3-20f** (both oils) was assigned by analysing the coupling constants of the C*H*OH and C*H*OTMP groups (Table 3.15).

Table 3.15 Significant NMR data of compounds **3-20f** and **3-20g**

Entry	Isomer	δ (ppm), multiplicity (*J* (Hz))			
		Cyclohexanone **3-20f**		Cycloheptanone **3-20g**	
		*CH*OH	*CH*OTMP	*CH*OH	*CH*OTMP
1	*cis*-**3-20**	4.18, br d (1.9)	3.65, ddd (11.5, 4.4, 2.7)	4.18, m	3.65, ddd (10.3, 3.2, 2.4)
		68.1, d	83.5, d	70.2, d	86.7, d
2	*trans*-**3-20**	3.76, m	3.76, m	3.91, m	3.91, m
		75.5, d	83.8, d	77.0, d	86.2, d

The hydrogen atom in C*H*OTMP in compound *cis*-**3-20f** appeared as a ddd with coupling constants 11.5, 4.4, 2.7 Hz, which means that the tetramethylpiperinyloxy unit is oriented in an equatorial position, since the axial hydrogen atom displays a $^3J_{aa}$ coupling constant of 11.5 Hz and 2 small $^3J_{ae}$ of 4.4 and 2.7 Hz only in this arrangement. For the C*H*OH group only one small coupling constant $^3J_{ae}$ or $^3J_{ee}$ of 1.9 Hz was determined unequivocally. However, the line width at half height is only about 10 Hz. This speaks in favour of 3 small coupling constants, thus the hydrogen atom in C*H*OH must be oriented equatorially. Consequently this compound has a *cis*-configuration. The line width at half height of the C*H*OH and C*H*OTMP groups in *trans*-**3-20f** is 18 Hz. This supports a *trans*-arrangement in *trans*-**3-20f**.

Scheme 3.13 Formation of the favoured *cis*-diastereomer



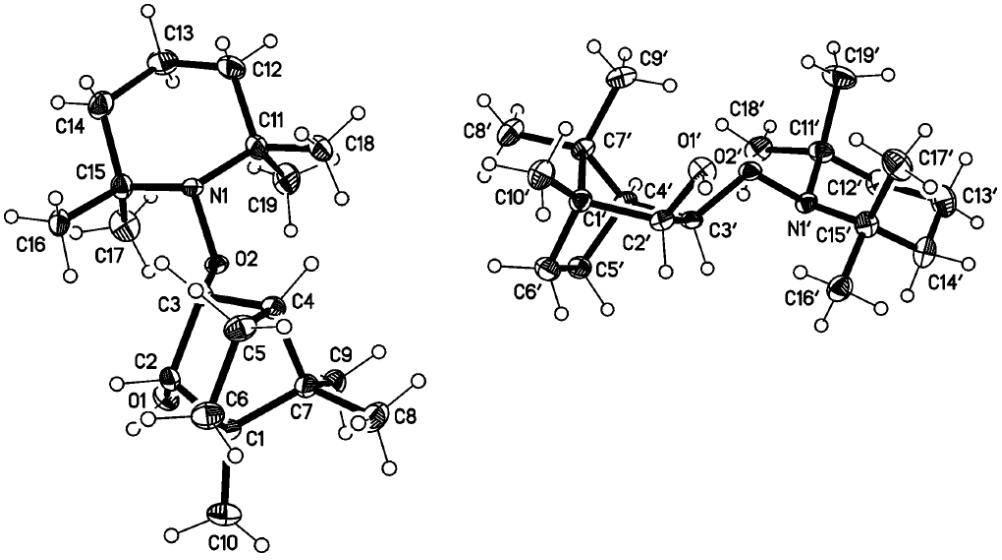
The more stable conformation **A** of α-(tetramethylpiperidinyloxy) cyclohexanone **3-11f** should be chair-like with the TMP-group oriented in the equatorial position (Scheme 3.13). The tetramethylpiperidinyl group rotates freely around the N-O bond. The less reactive reagent $NaBH_4$, approached the cyclohexane ring more selectively with a trajectory *anti*-orientated to the tetramethylpiperidinyloxy group giving *cis*-**3-20f**. The attack from the other side is however also possible, giving a moderate 2.7:1 *cis/trans* ratio. The more reactive $LiAlH_4$ does not differentiate both faces of the carbonyl group leading to a 1:1.1 *cis/trans* mixture. The cycloheptane ring induced better selectivities in the reduction of α-(tetramethylpiperidinyloxy)cycloheptanone **3-11g** by both reagents. $NaBH_4$ gave a better diastereoselectivity than $LiAlH_4$.

The reduction of *(R)*-Camphor **3-10h** by hydrides occurs normally from the *endo*-face and provides isoborneol as the major product.[105] Chiral α-(tetramethylpiperidinyloxy) *(R)*-camphor 3-*exo*-**3-11h** and 3-*endo*-**3-11h** were interesting substrates to study the course of the reduction under sterically more constrained conditions.

The substrate 3-*exo*-**3-11h** was completely recovered after treatment with $NaBH_4$ at 0 °C (Table 3.13, entry 9). In contrast 3-*exo*-**3-11h**, containing small amounts of 3-*endo*-**3-11h**, was reduced by $LiAlH_4$ with complete diastereoselectivity, providing 2-*exo*,3-*exo*-**3-20h** in high yields (entries 10 and 11). Reduction of 3-*endo*-**3-11h** at 0 °C to room temperature gave 2-*endo*,3-*endo*-**3-20h** and 2-*exo*,3-*endo*-**3-20h** in 100% yield with a 4.6:1 d.r. (entry 12).

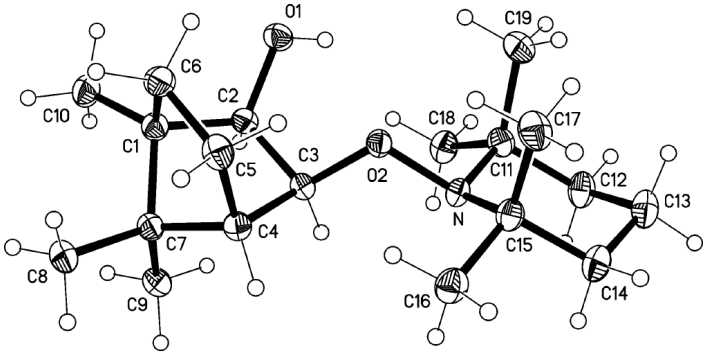
The configuration of 2-*exo*,3-*exo*-**3-20h** was unequivocally proved by X-ray crystallography (Figure 3.3). Both substituents are located on the *exo*-face of the bicyclus. No hydrogen bonds were observed. The elementary cell contains two molecules.

Figure 3.3 X-Ray crystal structure of 2-*exo*,3-*exo*-**3-20h**.



The configuration of 2-*endo*,3-*endo*-**3-20h** was also confirmed by an X-ray crystal structure (Figure 3.4). Both the hydroxy group and the tetramethylpiperidinyloxy group are found on the *endo*-side of the ring system. The tetramethylpiperidine ring having a chair conformation is oriented away from the bridged bicycle.

Figure 3.4 X-Ray crystal structure of 2-*endo*,3-*endo*-**3-20h**



Additionally the isomers 2-*exo*,3-*exo*-**3-20h**, 2-*endo*,3-*endo*-**3-20h** and 2-*exo*,3-*endo*-**3-20h** were compared with respect to their ^{1}H and ^{13}C NMR chemical shifts of positions 2, 3 and 4 and their coupling constants with 2-*exo*,3-*exo*-camphane-2,3-diol **3-21** and 2-*endo*,3-*endo*-camphane-2,3 diol **3-22**, respectively (Table 3.16 and 3.17).[106] The chemical shifts, multiplicities and coupling constants of H2 and H3 are similar for the pairs of compounds 2-*exo*,3-*exo*-**3-20h**/2-*exo*,3-*exo*-**3-21** (Table 3.16, entries 1 versus 2) and 2-*endo*,3-*endo*-**3-20h**/2-*endo*,3-*endo*-**3-22** (entries 3 versus 4). The shifts of H4 are less similar. The ^{1}H NMR data of 2-*exo*,3-*endo*-**3-20h** differ strongly from the *exo,exo* and *endo,endo* isomers.

Table 3.16 Comparison of ^{1}H NMR data of **3-20h**, **3-21** and **3-22**

Entry	Compound	δ (m, *J* (Hz))			
		H2	OH	H3	H4
1	2-*exo*,3-*exo*-**3-20h**	3.58 (dd, 7.4, 3.7)	3.12 (d, 3.9)	3.92 (d, 7.4)	2.14 (d, 5.1)
2	2-*exo*,3-*exo*-**3-21**[106]	3.51 (d, 7.0)	-	3.84 (d, 7.0)	1.70 (d, 4.7)
3	2-*endo*,3-*endo*-**3-20h**	3.77 (ddd, 9.3, 5.0, 1.8)	2.84 (d, 5.0)	4.20 (ddd, 9.4, 4.4, 2.0)	1.97 (t, 4.5)
4	2-*endo*,3-*endo*-**3-22**[106]	3.80 (dd, 8.8, 1.9)	-	4.21 (m, 8.8, 4.6, 1.5)	1.85 (m, 4.6, 4.6)
5	2-*exo*,3-*endo*-**3-20h**	4.28 (dt, 4.5, 2.3)	1.69 (s)	3.53 (s)	2.06 (t, 4.3)

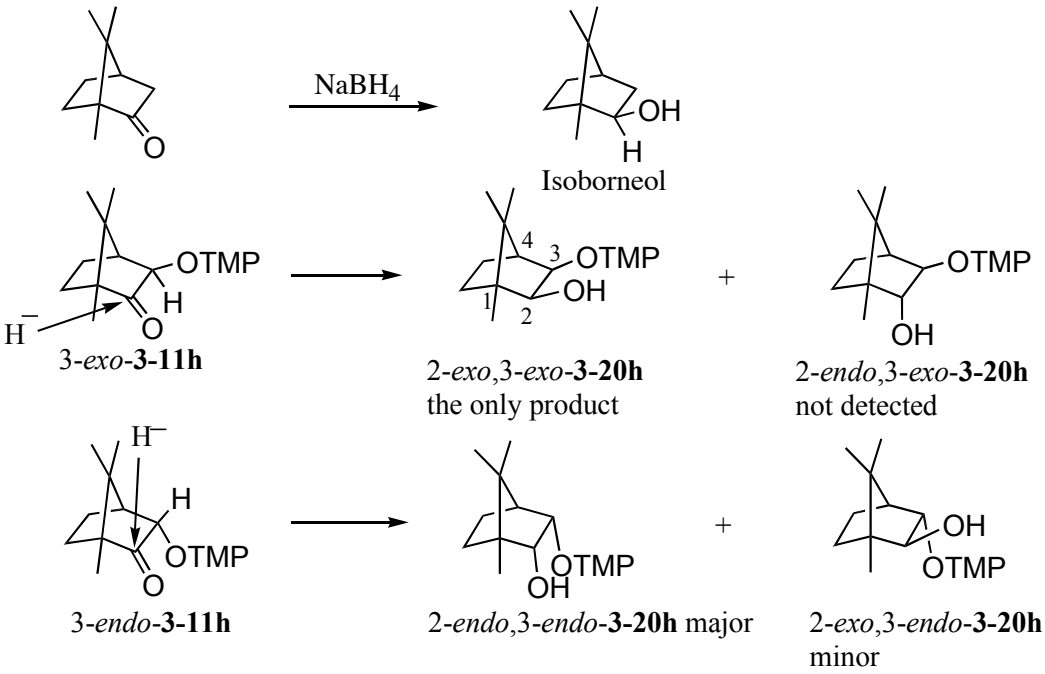
A striking similarity of the ^{13}C chemical shifts for C1 and C2 was observed for the pairs 2-*exo*,3-*exo*-**3-20h**/2-*exo*,3-*exo*-**3-21** (Table 3.17 entries 1 versus 2) and 2-*endo*,3-*endo*-**3-20h**/2-*endo*,3-*endo*-**3-22** (entries 3 versus 4). The presence of the tetramethylpiperidinyloxy group induced more significant differences for C3 and C4.

Table 3.17 Comparison of ^{13}C NMR data of **3-20h**, **3-21** and **3-22**

Entry	Compound	δ (ppm, multiplicity)			
		C1	C2	C3	C4
1	2-*exo*,3-*exo*-**3-20h**	46.28 (s)	79.93 (d)	90.81 (d)	48.69 (d)
2	2-*exo*,3-*exo*-diol **3-21**	46.43 (s)	79.93 (d)	79.19 (d)	51.47 (d)
3	2-*endo*,3-*endo*-**3-20h**	43.63 (s)	73.74 (d)	82.95 (d)	49.32 (d)
4	2-*endo*,3-*endo*-diol **3-22**	44.37 (s)	73.71 (d)	84.58 (d)	52.46 (d)
5	2-*exo*,3-*endo*-**3-20h**	46.49 (s)	86.27 (d)	94.88 (d)	49.80 (d)

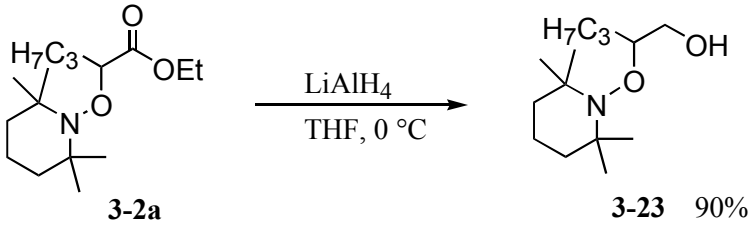
The reduction of *(R)*-camphor occurs from the endo-face yielding isoborneol. Similarly compound 2-*exo*,3-*exo*-**3-20h** was obtained as the only diastereomer. The tetramethylpiperidinyloxy and bridge methyl groups blocked the *exo*-side completely, allowing hydride attack only from the *endo*-face (Scheme 3.14). In 3-*endo*-**3-11h** the approach from the *endo*-face is hindered by the neighbouring tetramethylpiperidinyloxy group to a high extent, therefore the hydride attack proceeded mainly from the *exo*-face, but the face selection is less pronounced, since some 2-*exo*,3-*endo*-**3-20h** was also isolated.

Scheme 3.14 Formation of preferred *cis*-diastereomers



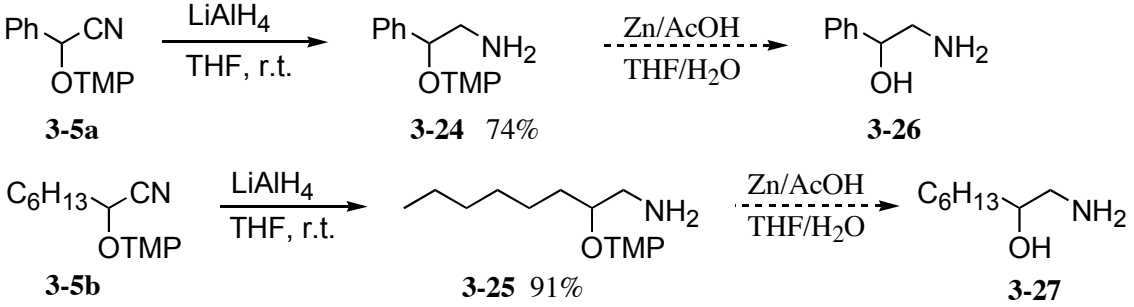
Terminal monoprotected 1,2-diol **3-23** was obtained by reduction of α-(tetramethylpiperidinyloxy)ester **3-2a** with $LiAlH_4$ in dry THF at 0 °C in high yield (Scheme 3.15).

Scheme 3.15 Reduction of ester **3-2a**



3-2a **3-23** 90%

Scheme 3.16 Reductions of nitriles **3-5b** and **3-5a** with hydrides



3-5a **3-24** 74% **3-26**

3-5b **3-25** 91% **3-27**

Reduction of α-tetramethylpiperidinyloxy nitriles **3-5a** and **3-5b** with $LiAlH_4$ proceeded efficiently forming α-tetramethylpiperidinyloxy amines **3-24** and **3-25**, which can

be potentially reductively deprotected to the free amino alcohols **3-26** and **3-27** (Scheme 3.16).

The structures of α-tetramethylpiperidinyloxy alcohol **3-23** and amines **3-24** and **3-25** were elucidated based on their NMR data. The positions bearing the tetramethylpiperidinyloxy group, the alcohol and respectively amine functionalities are characteristic for these compounds (Table 3.18).

Table 3.18 Significant chemical shifts of products **3-23**, **3-24** and **3-25**

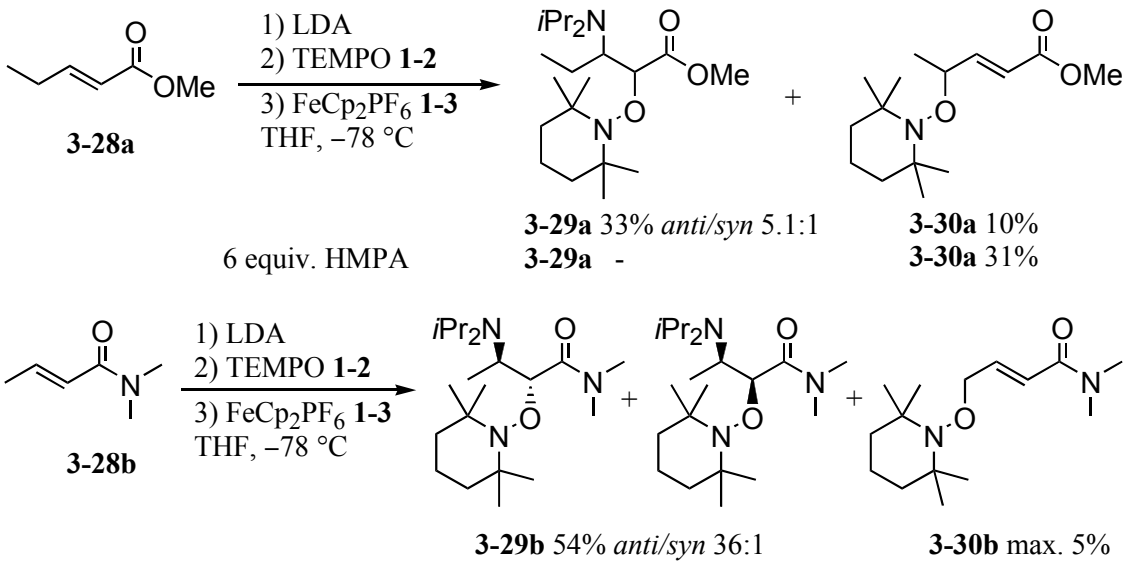
Entry	Compound	δ (ppm, multiplicity)	
		*CH*OTMP	CH_2OH or CH_2NH_2
1	**3-23**	4.20 (dddd), 79.8 (d)	3.89 (dd), 68.6 (t)
2	**3-24**	4.69 (t), 87.9 (d)	3.11 (d), 46.6 (t)
3	**3-25**	3.76 (m), 83.2 (d)	2.82 (m), 44.8 (t)

Key results: α-Tetramethylpiperidinyloxy ketones, esters and nitriles **3-2**, **3-5** and **3-11** can be efficiently reduced to monoprotected diols like **3-20** and **3-23** and protected amino alcohols like **3-24** and **3-25** by hydrides. Reduction of aromatic, bicyclic chiral and racemic α-tetramethylpiperidinyloxy ketones occurred with good to high diastereoselectivities.

3.3. Reactivity of α,β-unsaturated carbonyl compounds with LDA, TEMPO and ferrocenium hexafluorophosphate

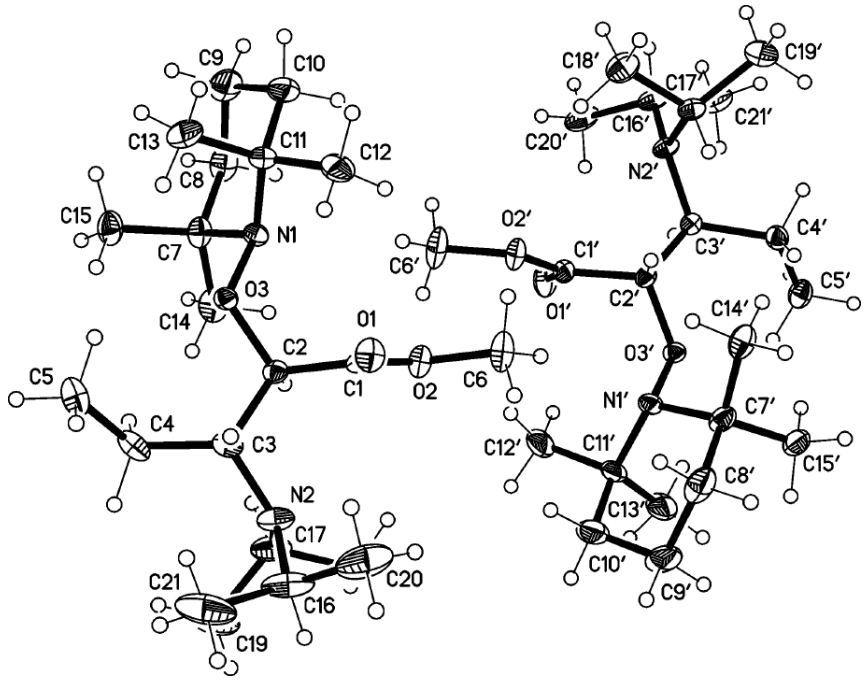
An interesting class of compounds eligible to the oxygenation with TEMPO were α,β-unsaturated carbonyl compounds, since potentially both α- and γ-TEMPO trapping can occur (Scheme 3.17). Reaction of methyl *trans*-2-pentenoate **3-28a** with LDA and subsequent oxygenation by TEMPO afforded surprisingly β-amino-α-TMPoxy ester **3-29a** in 33% yield and γ-coupling product **3-30a** in only 10% yield. Product **3-29a** was obtained with good 5.1:1 *anti/syn* diastereoselectivity. The regioselectivity switched in the presence of HMPA completely, affording only γ-oxygenated product **3-30a**, but the yield of 31% was low. *N,N*-Dimethyl crotonamide **3-28b** provided product **3-29b** in 54% yield with 36:1 *anti/syn* diastereoselectivity. Oxygenation product **3-30b** was isolated only in maximal 5% yield with low purity. Reactions in the presence of HMPA gave complex mixtures, from which no defined products were isolated. Deprotonation and oxidation of 2-cyclohexenone and 2-pentenenitrile with ferrocenium hexafluorophosphate **1-3** in the presence of TEMPO **1-2** afforded complex mixtures under the same conditions.

Scheme 3.17 Tandem conjugate addition/oxygenation versus oxygenation of **3-28a** and **3-28b**



The major *anti*-diastereomer of **3-29a** was unambiguously assigned by X-ray crystallography (Figure 3.5). The compound crystallised having an (*R,R*)- and (*S,S*)-configurated molecule in the unit cell. Both enantiomers are arranged in a staggered conformation, in which the bulky diisopropylamino and tetramethylpiperidinyloxy groups are arranged antiperiplanar.

Figure 3.5 X-Ray crystal structure of *anti*-**3-29a**



The configuration of the major diastereomer of **3-29b** was assigned to be *anti* by comparison of the NMR data with *anti*-**3-29a**. The ^{1}H NMR chemical shift of the C*H*OTMP group is shifted to the lower field for *anti*-**3-29b** compared to *syn*-**3-29b**. Significant NMR data of the products are presented in Table 3.19.

Table 3.19 ^{1}H and ^{13}C NMR chemical shifts of compounds **3-29a** and **3-29b**

Entry	Isomer	δ (ppm), multiplicity (*J* (Hz))	
		*CH*OTMP	*CH*N*i*Pr$_2$
1	*anti*-**3-29a**	4.42 (d, 10.0), 86.7 (d)	3.07 (m), 59.2 (d)
2	*syn*-**3-29a**	4.19 (d, 5.2), 88.1 (d)	3.26 (ddd, 9.0, 5.1, 3.8), 58.2 (d)
3	*anti*-**3-29b**	4.57 (d, 9.9), 78.9 (d)	3.62 (dq, 9.1, 7.0), 52.5 (d)
4	*syn*-**3-29b**	4.47 (d, 8.1)	Not detectable.

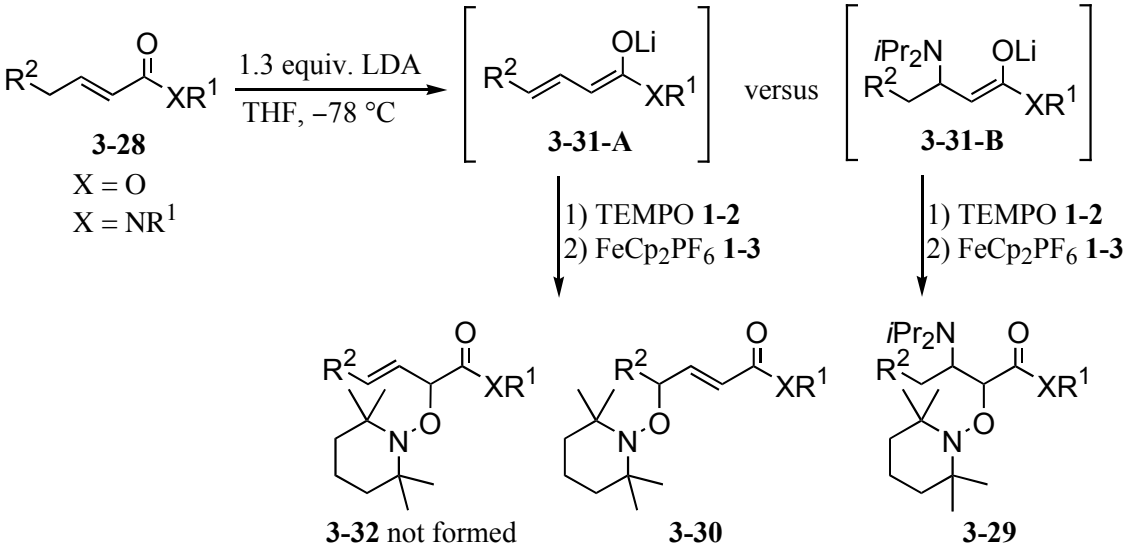
The structure of byproducts **3-30a** and **3-30b** was assigned based on their NMR data. The position bearing the TMPOxy-functionality and the double bond were characteristic for these compounds.

Table 3.20 Significant chemical shifts of products **3-30a** and **3-30b**

Entry	Isomer	δ (ppm), multiplicity		
		CH$_x$OTMP (x =1 or 2)	*CH*=CHCOO	*CH*COO
1	**3-30a**/^{1}H NMR	4.44 (quint)	6.98 (dd)	5.91 (d)
2	**3-30a**/^{13}C NMR	78.4 (d)	150.6 (d)	118.6 (d)
3	**3-30b**/^{1}H NMR	4.47 (dd)	6.84 (dt)	6.54 (dt)
4	**3-30b**/^{13}C NMR	76.2 (t)	140.8 (d)	119.2 (d)

Competing deprotonation in γ-position giving enolate **3-31-A** and conjugate addition of the amide anion leading to **3-31-B** occurred (Scheme 3.18). Oxidation and regioselective trapping by TEMPO at the more electron rich γ-position gave **3-30** from **3-31-A**. Although LDA is a bulky base, Michael addition[107] to the double bond competed significantly giving enolate **3-31-B**. Subsequent SET oxidation and trapping by TEMPO afforded products **3-29**. The presence of HMPA suppressed the Michael addition of LDA to methyl *trans*-2-pentenoate **3-28a** affording only product **3-30a**, although the yields remained low. For *N,N*-Dimethyl crotonamide **3-28b** Michael addition prevailed almost completely over deprotonation, affording the Michael addition/oxidation/TEMPO trapping product **3-29b.**

Scheme 3.18 Mechanism of product formation with α,β-unsaturated substrates **3-28**



3-28
X = O
X = NR[1]

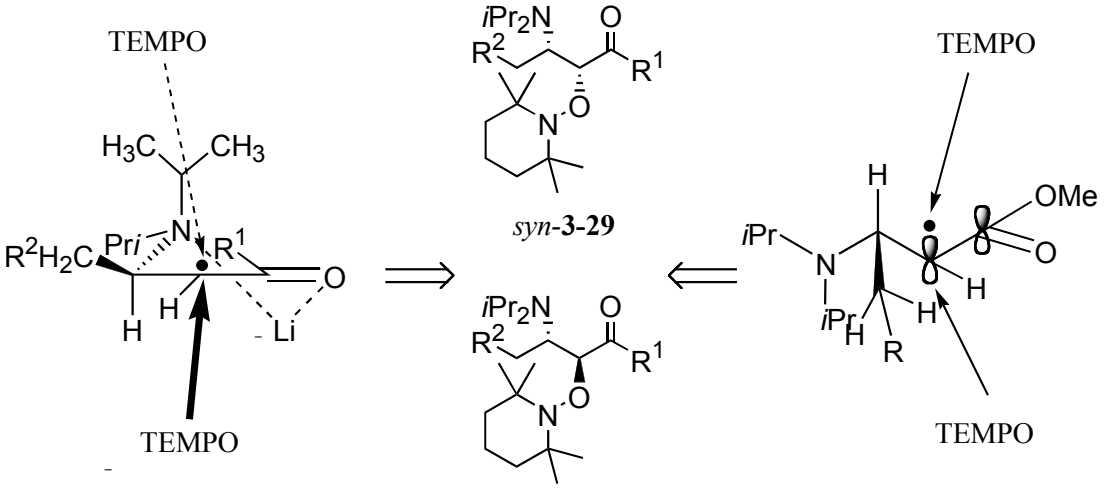
3-31-A **3-31-B**

3-32 not formed **3-30** **3-29**

The *anti*-diastereoselectivity of the TEMPO trapping can be rationalised as follows. The enolate resulting after conjugate addition forms a six-membered chelate. On SET oxidation this chelate remains largely intact and gives radical **3-33-A**, which exists because of the planar geometry of the α-carbonyl radical probably in a cyclohexene-like conformation **3-33-A** (Scheme 3.19).

The approach of TEMPO from the α-face is more favourable, leading to the formation of the major *anti*-diastereomer. Breaking of the chelate on oxidation and relaxation of the radical as in **3-33-B** would probably lead to almost equal formation of both diastereomers.

Scheme 3.19 Formation of preferred *anti*-diastereomer



syn-**3-29**

3-33-A *anti*-**3-29** favoured **3-33-B**

Key results: This reaction has a methodic potential. Detailed investigations are necessary to improve the control over the switch between sequential Michael addition/SET oxidation/TEMPO trapping and deprotonation in γ-position/SET oxidation/TEMPO trapping leading either to β-amino-α-tempoxy carbonyl compounds **3-29** or to γ-tempoxy α,β-unsaturated carbonyl compounds **3-30**.

3.4. Attempted α-oxygenations of carbonyl compounds with oxygen

A more direct method to introduce oxygen in the α-position of carbonyl compounds is oxidative coupling of enolates with oxygen (Scheme 3.20).[13, 108] The enolate of ethyl heptanoate **3-1d** generated by deprotonation with LDA in THF was treated with O_2 by bubbling a dry oxygen stream into the enolate solution for a given time. The substrate was recovered to 65%. No other products were detected (Table 3.21, entry 1). This indicates that lithium enolates are rather insensitive to oxygen. To promote oxygenation, LiCl was added to modify the enolate aggregates and the time of oxygen bubbling was reduced to 30 minutes.

Scheme 3.20 Oxygenation of the enolate of **3-1d** with O_2

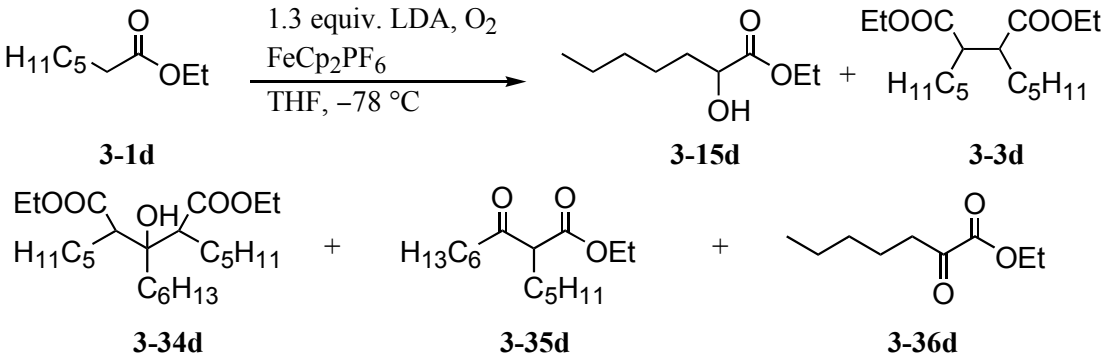


Table 3.21 Oxygenation of **3-1d** by bubbling dry oxygen at −78 °C

Entry	Deprotonation (min)/ O_2 bubbling (min)	Additive	**3-1d** (%)	**3-15d** (%)	**3-34d** (%)	**3-35d** (%)
1	30/60	-	65	-	-	-
2[a]	30/30	LiCl	8	12	19	11
3	90/30	LiCl	3	-	46	14
4	90/30	LiCl	3	-	53	13

a) 1% **3-3d** detected.

Under these conditions ethyl α-hydroxy heptanoate **3-15d** was indeed isolated in 12% yield. It was, however, accompanied by products **3-34d** and **3-35d** formed via anionic pathways (entry 2). Longer deprotonation times favoured the formation of **3-34d** and **3-35d** derived from anionic processes in moderate yields, however, no **3-15d** was formed (entries 3 and 4).

Formation of **3-15d** showed that the enolate was oxidised by O_2, nonetheless the reaction was very inefficient (Table 3.21, entry 2). Therefore the product distribution was investigated at different oxygenation times (Table 3.22). To promote radical coupling and the complete disappearance of the enolate, ferrocenium hexafluorophosphate **1-3** was added, after bubbling a pre-dried oxygen stream. In its presence ester enolates underwent instantaneous oxidative coupling to dimers **3-3d** (*vide infra*).

Table 3.22 Oxygenation of enolate of **3-1d** by bubbling dry O_2, followed by addition of $FeCp_2PF_6$.

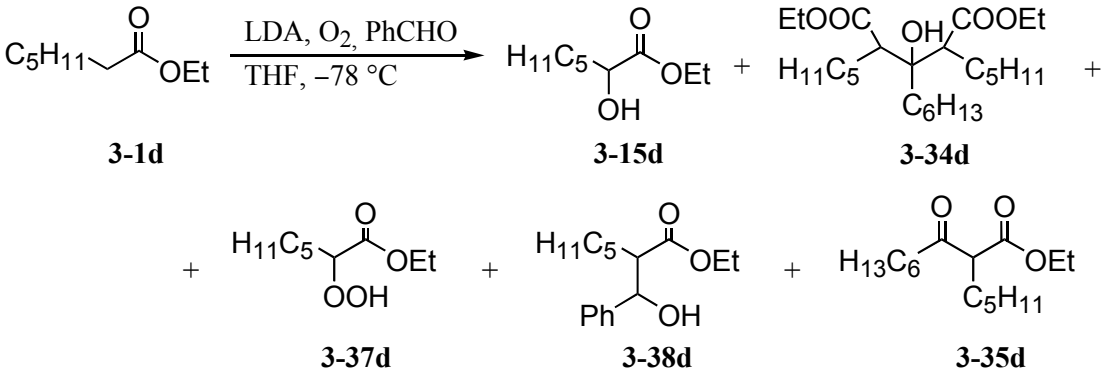
Entry	O_2 bubbling Time/T	**3-1d** (%)	**3-3d** (%, *meso/d,l*)	**3-15d** (%)	**3-34d** (%)	**3-35d** (%)	**3-36d** (%)
1	10 min/−78 °C	-	26 (1:1)	5	4	2	-
2	30 min/−78 °C	14	-	29	5	4	-
3	60 min /−78 °C	3	2 (1:0)	14	-	-	-
4[a]	60 min /−30 °C	-	-	14	38	-	2
5	60 min /−30 °C	4	10 (1:1)	11	26		4
6[b]	60 min /−40 °C	51	-	14	22		2

a) Deprotonation at −30 °C. b) In the presence of PPh_3.

In this way all enolate units that did not react with oxygen and did not undergo anionic reactions to **3-34d** and **3-35d** dimerised. In experiments with short oxygen bubbling time of 10 minutes the α-hydroxy ester **3-15d** was isolated in 5% yield while the dimer was formed in 26% yield (entry 1). Oxygen bubbling for 30 min yielded **3-15d** in 29% yield (entry 2). Oxygen bubbling for one hour at −78 °C afforded **3-15d** in only 14% yield, while **3-34d** or **3-35d** were not detected (entry 3). The low temperature of −78 °C suppressed Claisen condensation reactions leading to **3-34d** and **3-35d**. Oxygen bubbling at higher temperatures favoured anionic pathways giving **3-34d** in 22 to 38% yield and **3-15d** in low yields of 11-14% (entries 4-6). Even when PPh_3 was used for reduction of the first formed peroxide, compound **3-15d** was obtained only in 14% yield (entry 6).

The direct oxygenation of ethyl heptanoate **3-1d** with oxygen was inefficient and the product distribution was not reproducible. The low mass balance is difficult to explain, since ethyl heptanoate has a high boiling point. To narrow the problem, benzaldehyde was added after bubbling oxygen for a given time to check whether any enolate was left in the solution (Scheme 3.21). Aldol additions of ester enolates to aldehydes are fast reactions. Thus, reaction of enolate of **3-1d** with benzaldehyde under aldol conditions in the presence of HMPA afforded **3-38d** and **3-35d** in 49% and 13% yield, respectively. HMPA was used to reduce anionic Claisen condensation to **3-35d** and further trimerisation to **3-34d**. The oxygenation reactions using varying deprotonation times of 30-45 min and oxygen bubbling times of 10-120 min gave similar results as above. The oxygenated product **3-15d** was formed in 0-29% yield, while **3-34d** was obtained in 0-36% and **3-35d** was isolated in 4-29% yield. In no case, aldol product **3-38d** could be isolated. This leads to the conclusion that the enolate was consumed by oxygen, before the addition of benzaldehyde and apparently this system is not suitable to monitor the process.

Scheme 3.21 Oxygenation of ester **3-1d** with O_2



3-1d **3-15d** **3-34d**

3-37d **3-38d** **3-35d**

Table 3.23 Conditions for oxygenation of ester **3-1d** with O_2

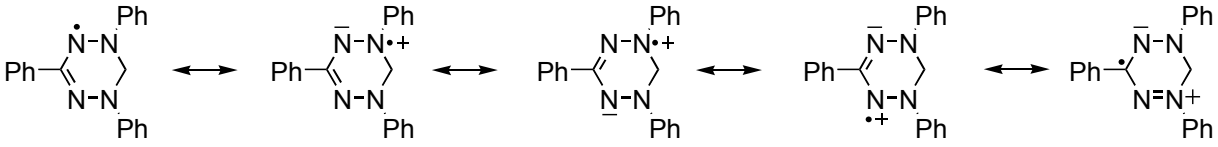
Entry	Deprotonation/ O_2 bubbling time	Additive	**3-1d**	**3-15d**	**3-34d**	**3-35d**	**3-38d**
1	30 min/ 0 min	HMPA	-	-	-	13	49
2	30 min/ 120 min	HMPA	3	6	trace	19	-
3	30 min/ 10 min	HMPA	9	29	-	4	-
4	45 min/ 10 min	HMPA	3	-	-	12	-
5	>30 min/ 10 min	HMPA	7	-	36	29	-

Key results: The oxygenation of ester enolates with oxygen occurred inefficiently, accompanied by a multitude of Claisen condensation processes.

3.5. Coupling of organometallic compounds with the free radical 1,3,5-triphenylverdazyl

A simple introduction of amine functionalities in the α-position of carbonyl compounds would give access to α-amino acids and other α-amino carbonyl compounds. To investigate the applicability of stable nitrogen radicals in coupling reactions, 1,3,5-triphenylverdazyl **3-39** was chosen.[109] 1,3,5-Triphenylverdazyl is a deep green solid. The delocalisation of the unpaired electron in the tetrazine system as well as conjugation with the benzene rings are the reasons for its stability (Figure 3.6). Generation of the enolate of a carbonyl compound and its oxidation by **1-3** in the presence of **3-39** should give compounds of type **2-10** (cf. Scheme 2.1). In contrast to TEMPO **1-2**, **3-39** has a lower oxidation potential than ferrocene (–0.22 V versus Fc/Fc^+),[110] which makes it susceptible to oxidation by **1-3**.

Figure 3.6 Electronic structure of 1,3,5-Triphenylverdazyl **3-39**



3.5.1. Synthesis of 1,3,5-triphenylverdazyl 3-39

1,3,5-Triphenylverdazyl was synthesised according to the literature procedure from triphenylformazane **3-40**[111] by treatment with methyl iodide in basic DMF under aerobic conditions (Scheme 3.22).[112] The synthesis was optimised as summarised in Table 3.24. To promote the first alkylation step the reaction mixture was stirred under nitrogen atmosphere in nitrogen-saturated DMF by bubbling a slight nitrogen stream for 6 h, followed by bubbling of an O_2 stream for 16 h or 68 h (entries 1, 2). The yields of 47% and respectively 58% were low to moderate. When the reagents where mixed and the reaction mixture was stirred open to the air for 64 h, 1,3,5-triphenylverdazyl **3-39** was isolated in a much improved 76% yield. The radical was purified by crystallisation, and the purity was checked by the melting point (136-139 °C) and combustion analysis. The mechanism can be formulated as follows: Triphenylformazane **3-40** is deprotonated by $Ba(OH)_2$ and the resulting anion is alkylated by methyl iodide. Oxidation of the tertiary amine **3-41** by oxygen to radical cation **3-42**, followed by a deprotonation to a terminal aminomethyl radical **3-43**, and subsequent radical 6-*endo* cyclisation to the azo group gives the persistent radical **3-39**.

Scheme 3.22 Synthesis of 1,3,5-trephenylverdazyl **3-39**

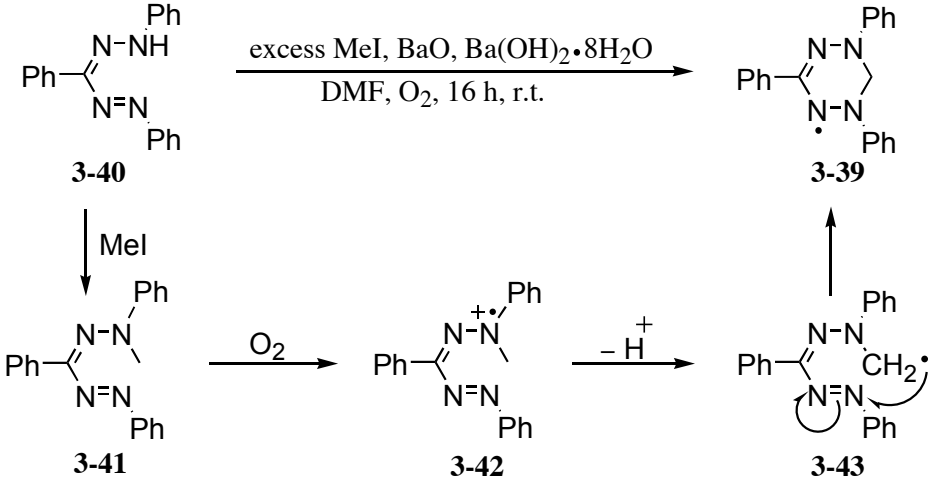


Table 3.24 Optimisation of 1,3,5-triphenylverdazyl **3-39** synthesis

Entry	Conditions	**3-39** (%)
1	N_2 bubbling 6 h, O_2 bubbling 16 h	47
2	N_2 bubbling 6 h, O_2 bubbling 68 h	58
3	Stirring open to the air for 64 h	76

3.5.2. Enolate oxidation and trapping with 1,3,5-triphenylverdazyl 3-39

Ethyl heptanoate **3-1d** was chosen for the investigations of radical amination reactions. Generation of the enolate by deprotonation with LDA, followed by oxidation with ferrocenium hexafluorophosphate **1-3** in the presence of **3-39** afforded product **3-44** in 64% yield based on **3-39** (Scheme 3.23, Table 3.25, entry 1). To avoid paramagnetic species in the product mixture, which would complicate NMR analysis, experiments were performed with 2 equivalents of enolate based on **3-39**. Interestingly two very similar sets of NMR signals were detected for compound **3-44**, indicating that compound **3-44** was isolated as mixture together with an unknown compound, which had a very similar structure. The striking similarity by NMR was confirmed by a successful combustion analysis from this mixture, which confirmed the chemical formula of **3-44** and of the unknown isomer being $C_{29}H_{34}N_4O_2$. A further structure elucidation failed. The dimer **3-3d** was isolated in 23% yield with a good 5:1 *meso/d,l*-diastereoselectivity. Small amounts of trimer **3-34d** were also detected. The coupling of the enolate of **3-1d** with verdazyl **3-39** in the presence of LiCl gave **3-44** and **3-3d** in similar yield, however, no diastereoselectivity was found for dimers **3-3d** (entry 2). Additionally compounds **3-34d**, **3-45** as well as disproportionation product **3-46** were detected by NMR spectroscopy in small amounts. The total efficiency of heterocoupling and homocoupling decreased when the SET oxidation was performed with $CuCl_2$ (entry 3).

Scheme 3.23 α-Amination of ethyl heptanoate **3-1d**

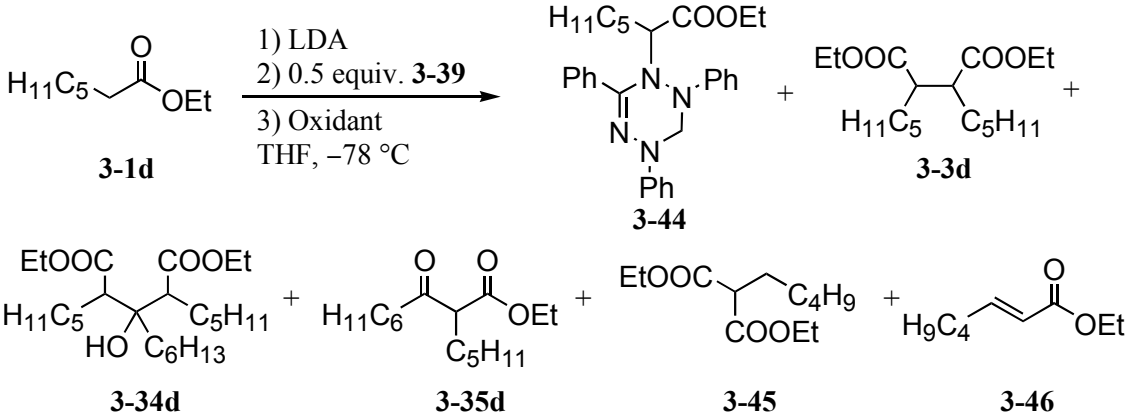


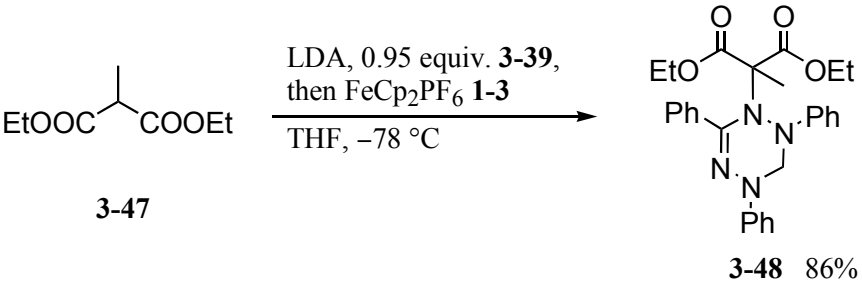
Table 3.25 α-Amination of ethyl heptanoate **3-1d**

Entry	Oxidant	Additive	**3-44**[a] (%)	**3-3d**[b] (%) (*meso/d,l*)	Other (%)
1[c]	$FeCp_2PF_6$	-	64	23 (5:1)	**3-34d** 3
2	$FeCp_2PF_6$	LiCl	60	22 (1:1)	**3-34d** trace, **3-45** 12, **3-46** 4
3	$CuCl_2$	-	54	3 (1:0)	**3-34d** trace, **3-35d** 3

a) Yields based on verdazyl **3-39**. b) Yields based on **3-1d**. c) Deprotonation at −50 °C.

The α-amination of diethyl methylmalonate **3-47** proceeded efficiently affording **3-48** in 86% yield as the only product (Scheme 3.24). This substrate is more hindered at the α-position and therefore much more resistant to anionic side reactions or dimerisation.

Scheme 3.24 α-Amination of diethyl methylmalonate **3-47**



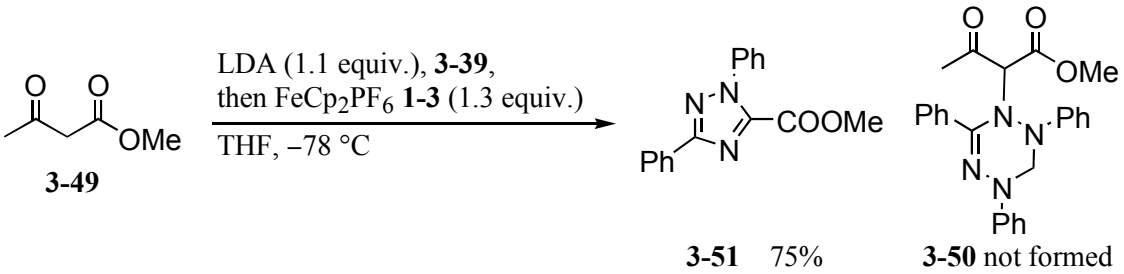
The structure of **3-44-I** and of **3-48** was elucidated based on their NMR data. In **3-44-I** and **3-44-II** (unknown isomer) there is only one hydrogen atom in the α-carbonyl position. The corresponding carbon is a doublet. In **3-48**, there is no hydrogen left in the α-carbonyl position and the carbon is a singlet. The complete verdazyl ring was unambiguously assigned for all three products.

Table 3.26 Significant NMR data of compounds **3-44-I**, **3-44-II** (unknown) and **3-48**

Entry	Compound	δ (multiplicity)		
		*CH*NNPh or *C*(CH_3)NNPh	Ph*C*=N	PhN*CH*$_2$NPh
1	**3-44-I**	4.15 (t), 64.2 (d)	150.3 (s)	4.34 (d), 5.28 (d), 63.2 (t)
2	**3-44-II**	4.33 (m), 64.4 (d)	149.4 (s)	4.37 (d), 5.49 (d), 64.8 (t)
3	**3-48**	- , 75.3 (s)	148.8 (s)	4.83 (d), 5.61 (d), 59.3 (t)

The reaction of verdazyl with methyl acetoacetate **3-49** under similar conditions provided a main product in high yield, whose analytical data do not correspond to the expected product **3-50** (Scheme 3.25).

Scheme 3.25 Radical amination of acetoacetate **3-49** with verdazyl



3-49

3-51 75%

3-50 not formed

The most likely structure assigned to the product was triazole **3-51** based on the following arguments. The NMR spectra revealed that the verdazyl ring was not present by comparison to **3-48**. The ring methylene group NCH_2N, well recognisable in the ^{1}H NMR spectra by an AB system in the range of 4.3-5.5 ppm and in ^{13}C NMR by a triplet around 60 ppm was missing.

The ^{1}H NMR spectra gave the following signals: a singlet at 3.95 ppm, a multiplet at 7.45 ppm, a singlet at 7.53 ppm and a multiplet at 8.22 ppm. The integral ratio was 3:5:3:2 speaking for a methoxy group and 10 aromatic protons. ^{13}C NMR gave a doublet or quartet at 53.2 ppm, which is an agreement with a methoxy group. Six doublets and two singlets at 129.6 and 137.9 ppm spoke for two phenyl rings. There are three more singlets at 145.0, 157.8 and 162.0 ppm. The resonances at 145.0 and 157.8 ppm were assigned to Ph*C*=N and N=*C*COOMe carbon atoms, respectively, while the resonance at 162.0 ppm was assigned to the carboxyl group. A strong intensity band at 1728 cm^{-1} in the IR spectrum also suggested the presence of an ester group in the molecule. In the MS (EI) spectrum peaks at 279 (100%) and 280 (15.6%), 281 (2.1%) were found. If one assigned peak 279 as the molecular ion, the ratio

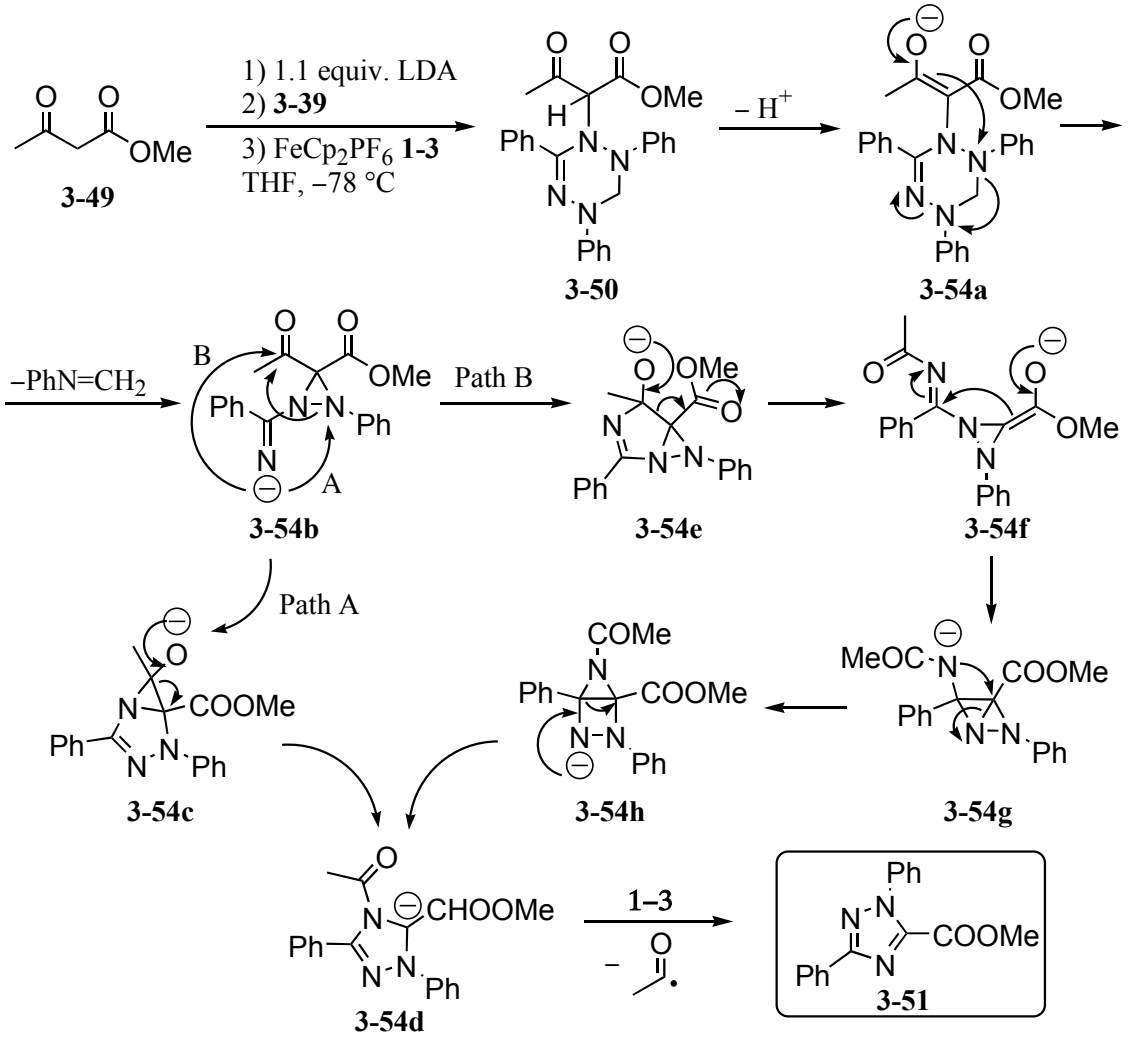
of peak heights $[M^+]/[M^+{+}1]$ gave the number of carbon atoms, which had to be 15.6. This information ascertained a compound with 16 carbon atoms. Based on these data, the reaction product has a 1,2,4-triazol structure like **3-51**. Other possible structures such as **3-52** or **3-53** are not likely based on the spectral data (Figure 3.7).

Figure 3.7 Potential alternative structures of the product triazoles **3-52** and **3-53**[113]

3-52 $C_{17}H_{17}N_3O$ M = 279.33

3-53 $C_{15}H_{13}N_3O$ M = 251.28

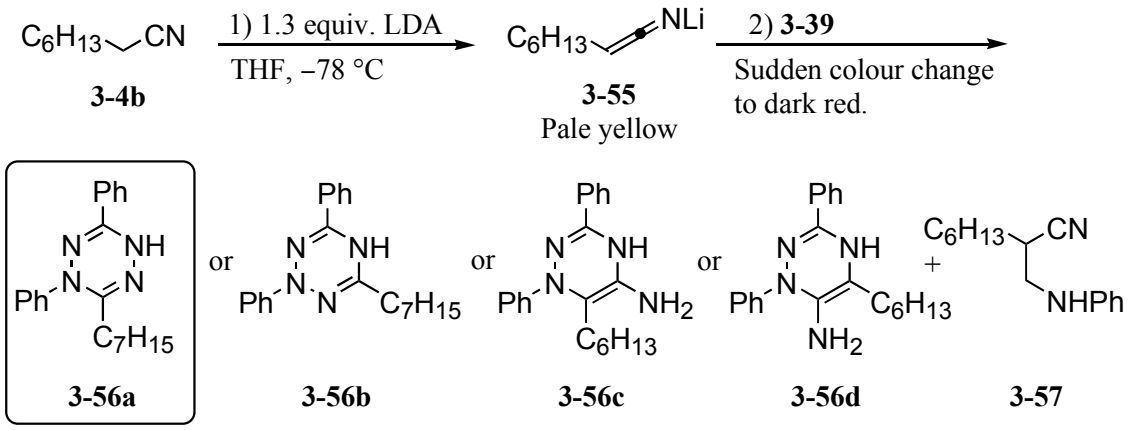
Scheme 3.26 Mechanism for the formation of **3-51**[114]



A possible mechanism can be proposed as depicted in Scheme 3.26, considering two possible pathways. Path A proceeds over 3 steps via less strained intermediates than path B that needs 4 steps. Therefore Path A seems more likely. It would be possible to distinguish these alternatives by ^{15}N labelling.

To extend the scope to other carbonyl derivates, α-amination of the ketene iminate **3-55** of octonitrile **3-4b** was investigated (Scheme 3.27). A sudden colour change from pale yellow of the solution to dark red at the addition of verdazyl (and not to deep green as usually) indicated a fast reaction. Workup at this stage afforded a mixture of two main compounds, which were not separable. In a second experiment the sequence was continued by addition of ferrocenium fluorophosphate, and the colour changed to dark blue. The same products were isolated. Thus no oxidation with ferrocenium hexafluorophosphate took place, but the mass balance was lower.

Scheme 3.27 Radical amination of octonitrile **3-4b**



The ring methylene group NCH_2N was completely missing in the ^1H and ^{13}C NMR spectra indicating a ring rearrangement reaction. The major product must be cyclic. Based on the NMR data, structures **3-56a-d** presented in Scheme 3.27 are possible. The minor component of the mixture was assigned to acyclic aminonitrile **3-57**.

Significant NMR data of the major product were assigned: a triplet at 0.85 for CH_3, two multiplets at 1.21-1.41 ppm for $CH_3(CH_2)_4$ and at 1.78 ppm for $N{=}CCH_2CH_2$. The integrals in the alkyl range are not accurate enough to determine the number of protons unambiguously. A multiplet at 2.82 ppm for $N{=}CCH_2$, and two multiplets at 7.34-7.57 ppm (8H) and at 8.15 ppm (2H) were assigned to the aromatic CHs. In the alkyl range of the ^{13}C NMR spectrum, the quartet was assigned to the terminal methyl group and 5 triplets to the saturated alkyl chain. In the aromatic range, 6 doublets were assigned to two phenyl rings.

The singlets of the phenyl ring could not be unambiguously detected. Two singlets at 157.0 and 161.3 ppm were assigned to the two carbon atoms of the tetrazine ring. Since NH or NH_2 groups were not conclusively detected in the spectrum, a distinction of **3-56a-d** is difficult. Since **3-56** and **3-57** are not separable, it is assumed, that based on the similar polarity only one NH group is present in the molecule. This aspect speaks rather in favour of **3-56a-b**, while **3-56c-d** should be much more polar. Based on these data, compound **3-56a** is the most probable product.

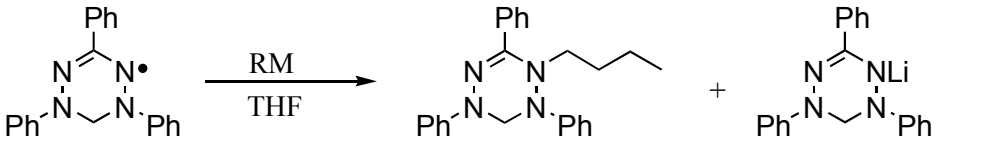
Compound **3-57** was unambiguously assigned: a multiplet (2H) at 3.38 ppm for CHC*H*$_2$NHPh, a broad singlet at 4.02 for N*H*Ph, a doublet (2H) at 6.60 ppm for aromatic CH, a triplet at 6.75 ppm for aromatic p-CH, and finally a dd (2H) at 7.20 ppm were the key resonances. Resonances in the alkyl range indicated a longer chain, while in ^{13}C NMR a singlet at 118.2 ppm was assigned to the cyano group.

3.5.3. Reactions of 1,3,5-triphenylverdazyl with organolithium, organozinc and Grignard reagents

In early studies alkyltetrazines were synthesised by coupling of 1,3,5-triphenylverdazyl with Grignard reagents or organolithium compounds.[115] Butyltetrahydrotetrazine **3-58a** was synthesised in 45% yield by treating 1,3,5-triphenylverdazyl **3-39** with 1 equivalent of BuLi (Scheme 3.28),[116] and the result proved to be reproducible (Table 3.27, entry 1). The complete consumption of verdazyl **3-39** was accompanied by a colour change from deep green to brown. It was noteworthy that the deep green colour of verdazyl reappeared during workup and some of it was recovered. Lowering the amount of BuLi to 0.5 equiv. did not lead to formation of **3-58a** (entry 2). The reaction was, however, improved by regenerating free **3-39** in situ from lithiumverdazyl **3-39-Li** by reoxidising it with dry air or dry oxygen. After reappearance of the green colour, the reaction mixture was purged with nitrogen and treated with additional BuLi at −78 °C. When the green colour of verdazyl turned to brown signalling its consumption, dry air was again bubbled through the solution until the colour changed to deep green. This procedure was repeated until the reaction mixture remained dark brown for at least 15 minutes of air bubbling. The yields increased to 86% (entry 3). This experiment was repeated also using dry oxygen for reoxidation of the verdazyl lithium species. The consumed amounts of BuLi were somewhat different giving **3-58a** in 92 and 85% yields, respectively (entry 4). This is probably due to exactness of addition and decomposition of excess BuLi by oxygen. The method was also applied to other organometallic reagents. The reactivity of *t*BuLi towards **3-39** proved to be

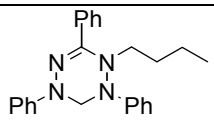
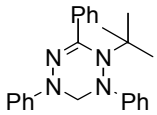
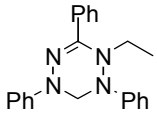
lower. Higher temperatures (−15 °C) and longer times were necessary to obtain a persistent colour change to brown of the verdazyl solution (entry 5). A total of 5.4 equivalents of *t*BuLi was used to reach the modest yield of 48% of **3-58b**.

Scheme 3.28 Reaction of verdazyl **3-39** with BuLi



3-39 **3-58a** 45-92% **3-39-M**
M = Li, MgBr, EtZn

Table 3.27 Reaction of verdazyl with organometallic compounds

Entry	Reagent (equiv.)	Product		Method/T (°C)	Yield (%)
1	BuLi (1)		**3-58a**	A/−30	45
2	BuLi (0.5)			A/20	0
3	BuLi (2.7)			B/−78	86
4	BuLi (1.8/3.9)			C/−78	92/85
5	*t*BuLi (5.4)		**3-58b**	C/−78	48
6	EtMgBr (1.83)		**3-58c**	C/−78	47
7	Et_2Zn (5.05)			C/0	47
8	$MgBr_2 \cdot Et_2O$	-	-	C/0 - 20	-

Method A: The organometallic reagent was added at once. Method B: **3-39** was alternatively titrated with the organometallic reagent and regenerated by bubbling dry air. Method C: **3-39** was alternatively titrated with the organometallic reagent and regenerated by bubbling dry oxygen.

EtMgBr was more reactive, but the reoxidation of organometallic species **3-39-MgBr** was not proceeding. After initial addition of 1.8 equivalents of EtMgBr, dry oxygen was bubbled through the solution but the reaction mixture did not change the colour back to green (entry 6). The yield of 47% was slightly higher than previously reported. The reaction with diethylzinc proceeded similarly, giving the product in 47% yield (entry 7).

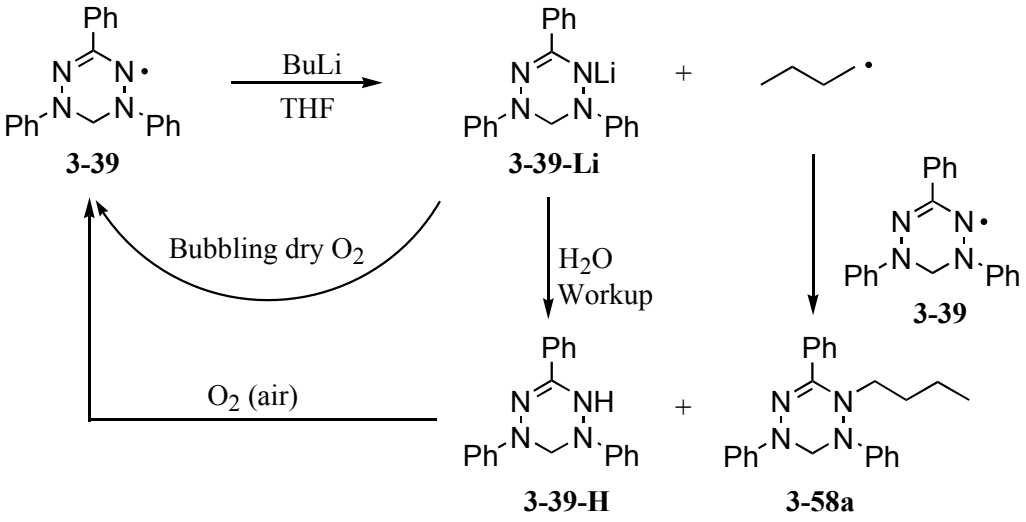
The structures of the products were assigned based on their NMR data (Table 3.28).

Table 3.28 Significant NMR data of compounds **3-58a-c**

Entry	Compound	δ (multiplicity)		
		CH$_2$NNPh or *C*NNPh	Ph*C*=N	PhN*CH*$_2$NPh
1	**3-58a**	3.22 (m), 55.1 (t)	149.0 (s)	4.24 (d), 5.54 (d), 57.7 (t)
2	**3-58b**	- , 60.7 (s)	150.0 (s)	4.73 (d), 5.78 (d), 62.0 (t)
3	**3-58c**	2.76 (br. s), 3.35 (br. s), 49.8 (t)	149.5 (s)	4.26 (d), 5.56 (d), 57.8 (t)

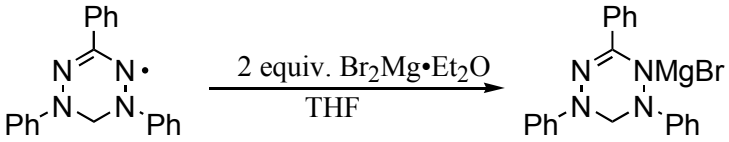
A plausible mechanism for the formation of alkyl verdazyl adducts **3-58a-c** is presented in Scheme 3.29. The verdazyl radical **3-39** oxidises the organometallic species giving **3-39-Li** and a butyl radical, which combines with the excess of **3-39** affording product **3-58a**. This explains the low yield of 45% obtained earlier in the reaction of equimolar amounts of verdazyl with BuLi. The reoxidation of **3-39-Li** to radical **3-39** by oxygen allowed the optimisation of the synthesis of **3-58a** up to 92% yield. Unfortunately BuLi was so far rather an exception, since either the coupling was slow, as in the case of *t*BuLi, or the reoxidation method was not as efficient for other organometallic reagents like EtMgBr or Et_2Zn.

Scheme 3.29 Mechanism of oxidation of organolithiums with verdazyl **3-39**



To determine whether stable verdazyl magnesium species can be generated individually, **3-39** was treated with two equiv. of $Br_2Mg{\cdot}OEt_2$ at 0-20 °C (Scheme 3.30). A colour change would indicate the reduction of the verdazyl. However, no colour change was observed and **3-39** was recovered, which indicated that it did not react with magnesium bromide.

Scheme 3.30 Treatment of **3-39** with $MgBr_2$.



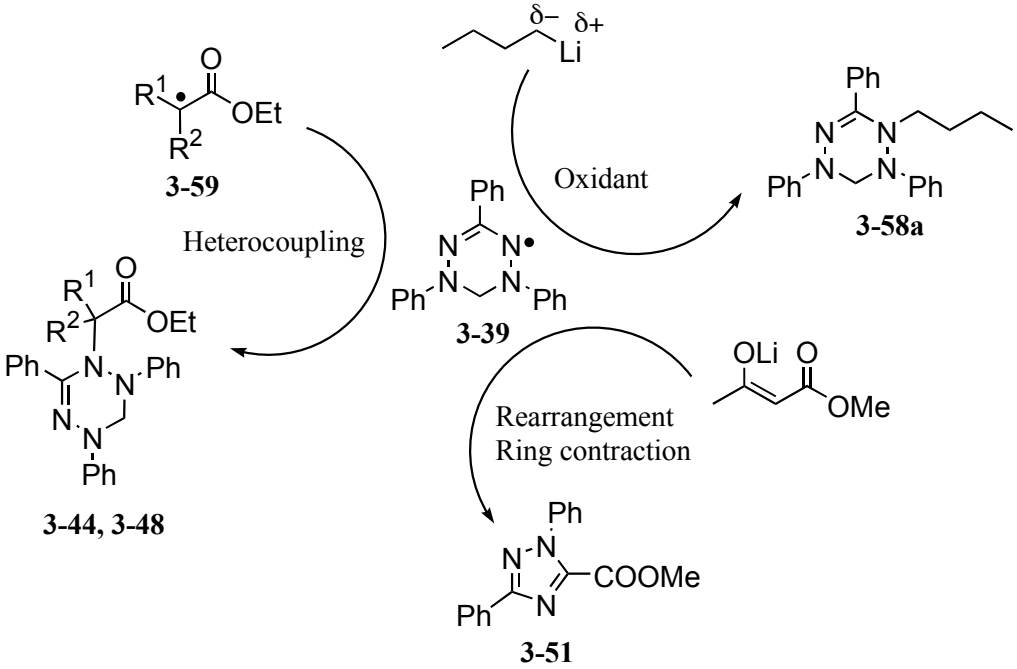
3-39 **3-39-MgBr**

Key results:

Investigations of the general reactivity of verdazyl **3-39** uncovered a multitude of reaction channels, which depend on the enolate structure (Scheme 3.31). The heterocoupling of verdazyl **3-39** with α-carbonyl radicals **3-59** was efficient and presented a new short access to α-amino carbonyl compounds **3-44** and **3-48** with nitrogen containing groups in α-position. With octonitrile **3-4b** and methyl acetoacetate **3-49** verdazyl underwent new rearrangement reactions. In the presence of the enolate of methyl acetoacetate **3-49**, the verdazyl ring contracted to triazole **3-51**, while **3-39** rearranged in the presence of a ketene iminate probably to tetrazine **3-56a**. These reactions are very interesting and deserve further investigation.

On the other hand **3-39** played the role of the oxidising agent in the reaction with organometallic reagents affording products of type **3-58a**. The reaction of **3-39** with BuLi was improved by reoxidising the coformed organometallic verdazyl species with oxygen, while for other organometallic reagents it proceeded rather with moderate yields. Further investigations are necessary to develop this reaction.

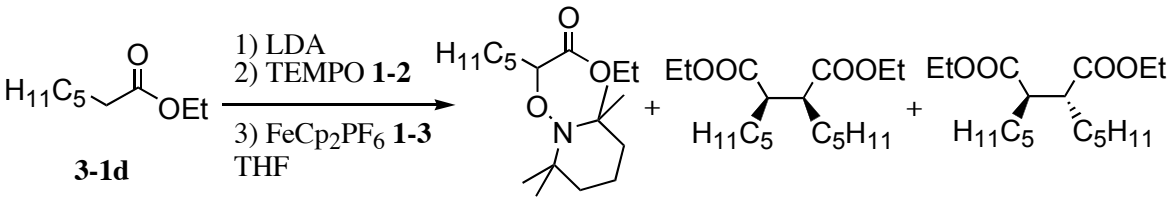
Scheme 3.31 Reactions of persistent radical verdazyl **3-39**



3.6. Dimerisations of carbonyl compounds

The radical dimerisation of carbonyl compounds competes surprisingly successfully to the trapping of α-carbonyl radicals **2-3** (cf. Scheme 2.1) with TEMPO for some ketones and esters although the latter was present in high concentration in the solution during oxidation, like for example ethyl heptanoate **3-1d** (Scheme 3.32).[10a] Due to the persistent radical effect,[46] dimerisation should not occur in these experiments under ordinary conditions. Moreover a diastereoselectivity was observed in the dimerisation of aromatic ketones and esters, which is surprising for enolates, which are not hindered or auxiliary bound.[62]

Scheme 3.32 α-Oxygenation of ethyl heptanoate **3-1** according to ref.[10a]



3-2d 42% **3-3d** 42% *meso/d,l* 1:1

The impact of enolate aggregation and additives on yield and diastereoselectivity of radical dimerisations will be studied under following aspects:

1. Investigation of different dimerisation conditions.
2. Applicability of the method for a large variety of carbonyl compounds.
3. Mechanistic investigations: a) Correlation of enolate geometry and diastereoselectivity. b) Influence of aggregation on diastereoselectivity to achieve better diastereoselectivity using supramolecular structures. c) Mechanism of the oxidation and coupling of enolates.

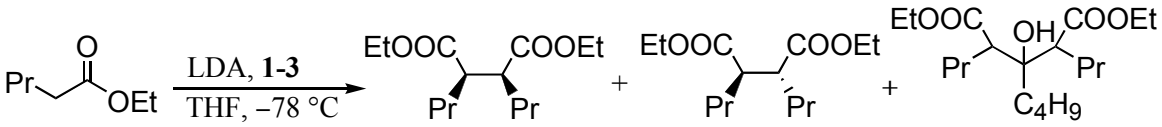
3.6.1 Investigation of different dimerisation conditions

The established dimerisation procedure developed for esters implies generation of the enolate by deprotonation with LDA in THF at −78 °C, followed by oxidation with ferrocenium hexafluorophosphate **1-3**.[10a, 25] Esters give often a moderate excess of the *meso*-dimer under these conditions. It is known that ester enolates form supramolecular structures in THF and that their enolates have (*E*)-geometry.[80, 81] However the enolate configuration can be changed to a (*Z*)-geometry by using HMPA as an additive.

The dimerisation diastereoselectivity of ethyl valerate **3-1a** was influenced by the addition mode of the oxidant **1-3** (Scheme 3.33). The dimer **3-3a** was obtained in 60% yield

in a 1.5:1 *meso/d,l*-ratio when two equivalents of ferrocenium hexafluorophosphate **1-3** were added at once to the enolate solution. When 1.8 equivalents of the oxidant **1-3** were added in small portions, the dimer **3-3a** was isolated in an improved 89% yield with a better 2.5:1 *meso/d,l*-ratio. The significance of these results for the mechanism is discussed in chapter 3.6.3 (*vide infra*).

Scheme 3.33 Dimerisation of **3-1a**



3-1a *meso*-**3-3a** *d,l*-**3-3a** **3-34a**

60% *meso/d,l* 1.5:1[a] 2%

89% *meso/d,l* 2.5:1[b]

a) The oxidant **1-3** (2 equiv.) was added at once to the enolate solution. b) The oxidant **1-3** (1.8 equiv.) was added in portions as it was consumed.

At higher temperature the diastereoselectivity of dimerisation decreased (Table 3.29, entry 1). Moreover trimerisation to **3-34a** competed. Interestingly, dimerisations in DME provided **3-3a** with reversed diastereoselectivity in moderate yields (entries 2 and 4). HMPA proved to be an additive of choice for breaking enolate aggregation in TEMPO trapping reactions. In an experiment in DME/HMPA 5.7:1 it displayed a detrimental effect, since only 16% of the desired dimer **3-3a** was isolated (entry 3).

Table 3.29 Dimerisation of **3-1a** under different conditions[a]

Entry	Solvent, additive, oxidation temperature	**3-3a** (%)	*Meso:d,l*	**3-34a** (%)
1	THF, –20 °C	53	1.2:1	25
2	DME, –78 °C	54	1:1.8	2
3	85% DME, 15% HMPA, –78 °C	16	-	-
4[b]	DME, 0.4 equiv. TEMPO, –78 °C	40	1:1.5	23

a) Deprotonation time 30 min, **1-3** was added in small portions. b) TEMPO trapping product **3-2a** was isolated in 29% yield; small amounts of Claisen condensation product were detected.

Other conditions were less suitable. Dimerisations in toluene afforded complex mixtures. Resonances of the dimers could not be detected by NMR spectroscopy. Attempted oxidative couplings of ethyl valerate enolate with $PdCl_2$ in THF in the absence or presence of 1 equivalent HMPA afforded also complex mixtures. Small amounts of products formed via

anionic pathways such as Claisen condensation product **3-35a** and trimer **3-34a** were detected. The transmetallation of the Li counter ion to a stronger chelating metal ion using $MgBr_2$ was tried, however, the magnesium enolate of ethyl valerate **3-1a** did not dimerise, but gave complex mixtures and a bad mass balance.

3.6.2. Substrate scope and correlation of the enolate geometry with the diastereoselectivity

The observation that esters enolates, which have an (*E*)-geometry in THF,[80] underwent oxidative couplings with *meso* selectivity,[10a] while propiophenone enolates with (*Z*)-geometry[1b] gave preferentially the *d,l*-dimer in high excess,[25] suggested the importance of the enolate geometry for the diastereoselectivity of dimerisations. The enolates of cyclohexanone **3-10f**, (*R*)-camphor **3-10h** and butyrolactone **3-1c** have a "frozen" *(E)*-geometry constrained by the ring (Scheme 3.34, Table 3.30). The dimerisation of cyclohexanone occurred in 86% yield but without diastereoselectivity (Table 3.30, entry 1). HMPA and LiCl as additives breaking aggregates decreased the yield somewhat, while the diastereoselectivity remained unchanged (entries 2 and 3).

Scheme 3.34 Dimerisation of cyclohexanone **3-10f** and (*R*)-camphor **3-10h**

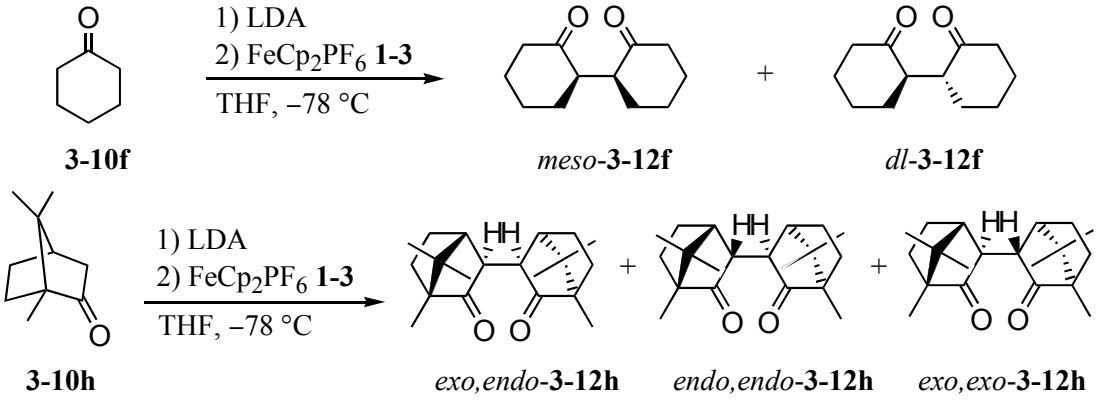


Table 3.30 Dimerisation of enolates with a "frozen" (*E*)-geometry.

Entry	Substrate	Additive (equiv.)	**3-12** (%)	Diastereoselectivity[a]
1	**3-10f**	-	**3-12f** 86	1:1.1[b]
2		LiCl (4.7)	**3-12f** 56[c]	1.2:1[b]
3		HMPA (6)	**3-12f** 67	1:1[b]
4	**3-10h**	-	**3-12h** 66	2.2:1.8:1[d]
5		-	**3-12h** 66	1.7:1:1.8[d]

a) The diastereomeric ratio was determined by NMR. b) *meso/d,l*. c) Additionally, 5% cyclohexenone was isolated. d) *exo,endo:endo,endo:exo,exo.*

The dimers of (*R*)-camphor **3-10h** were synthesised in good yields (entries 4 and 5).[117] The diastereoselectivity was modest and variable. Butyrolactone **3-1c** did not dimerise. The isolated complex mixtures may be attributed to ring-opening reactions.

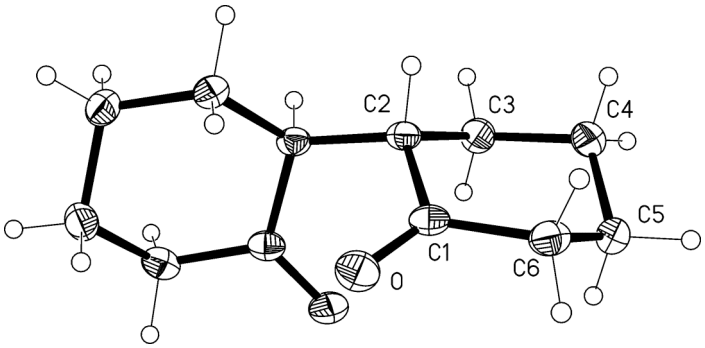
The structures of the dimers were assigned by means of their NMR data. The characteristic resonances of the α-carbonyl positions are given in Table 3.31.

Table 3.31 Significant NMR data of dimers **3-12f** and **3-12h**

Entry	Dimer	δ (ppm, multiplicity)	
		*CH*CO	CH_2*CH*CHCO
1	***d,l*-3-12f**	2.83 (m), 48.9 (d)	-
2	***meso*-3-12f**	2.63 (m), 50.1 (d)	-
3	***3,3'-endo,endo*-3-12h**	2.43 (m), 49.1 (d)	1.96 (m), 49.0 (d)
4	***3,3'-endo,exo*-3-12h**	2.35 (t), 46.6 (d), *exo*-part	2.67 (d), 46.5 (d), *exo*-part
		2.42 (m), 51.6 (d), *endo*-part	1.87 (m), 51.7 (d), *endo*-part
5	***3,3'-exo,exo*-3-12h**	2.00 (s), 54.2 (d)	2.08 (d), 46.8 (d)

The configuration of the isomer *d,l*-**3-12f** was established by X-ray crystal structure analysis (Figure 3.8). The stereochemistry of camphor dimers **3-12h** was assigned by NOE and NOESY experiments, and were in accordance with the NMR data known from the literature.[117]

Figure 3.8 X-Ray crystal structure of *d,l*-**3-12f**



It is known that the (*E*)-enolate geometry of esters in THF can be changed to the (*Z*)-enolate by using cosolvents such as HMPA or DMPU.[81] Dimerisations performed in 77% THF/23% HMPA as a classical solvent to reverse the ester enolate geometry and using LiHMDS as a base afforded complex mixtures (not shown). The oxidative coupling of the *(Z)*-enolate of **3-1a** in 55% THF/45% DMPU gave no dimer, instead complex mixtures were isolated (not shown).

Scheme 3.35 Dimerisation of (*Z*)-enolates

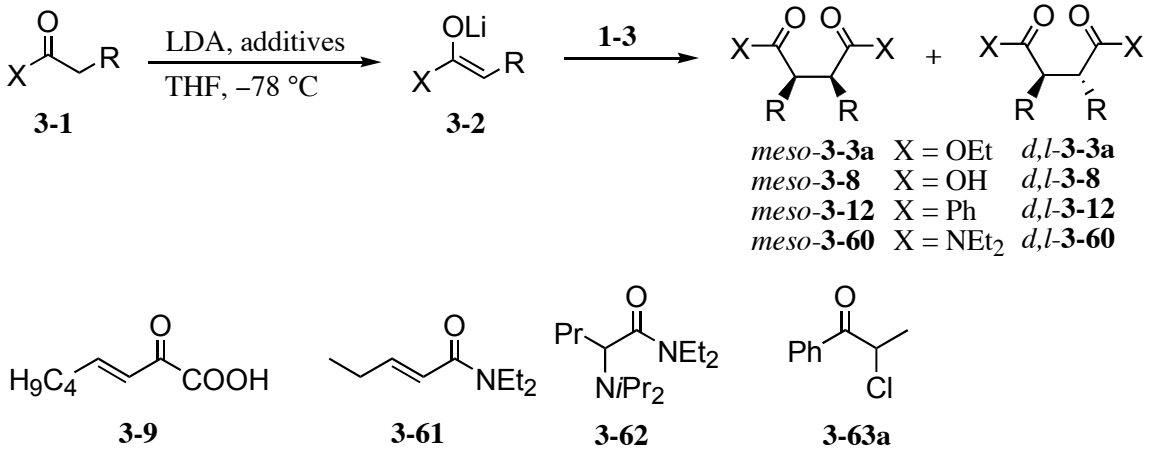


Table 3.32 Dimerisation of (*Z*)-enolates[a]

Entry	Substrate	R	X	Dimer (%)	*d,l/meso*	Other products (%)
1	**3-1a**	C_3H_7	OEt	**3-3a** 41	1.4:1	
2	**3-4d**	C_3H_7	NEt_2	**3-60** 40	2.5:1	**3-61** (7), **3-4d** (17)
3	**3-4d**	C_3H_7	NEt_2	**3-60** 30	2.1:1	**3-61** (6), **3-4d** (15)
4[c]	**3-4d**	C_3H_7	NEt_2	**3-60** 21	5:1	**3-62** (15), **3-4d** (9)
5[d]	**3-4d**	C_3H_7	NEt_2	**3-60** 19	1:0	**3-62** (12), **3-4d** (6)
6	**3-6**	C_5H_{11}	OH	**3-8** 33	4:1	**3-9** (15), **3-6** (51)
7[25]	**3-10a**	CH_3	Ph	**3-12a** 52	10:1	-
8[e]	**3-10a**	CH_3	Ph	**3-12a** 73	5.5:1	-
9[f]	**3-10a**	CH_3	Ph	**3-12a** 98	4.1:1	-
10[g]	**3-10a**	CH_3	Ph	**3-12a** 36	11:1	**3-63a** (12)
11	**3-10b**	CH_2CH_3	Ph	**3-12b** 84	> 13:1	-

a) If not otherwise stated, deprotonation was performed with 1.3 equiv. LDA, and oxidation was performed with **1-3**. b) Additive HMPA (6 equiv.). c) Deprotonation was performed with 2.3 equiv. LDA for 15 min. d) Deprotonation was performed with 2.3 equiv. LDA for 15 min, followed by 1 equiv. BuLi for 0.5 h. e) Additive LiCl (4.7 equiv.). f) Additive HMPA (6 equiv.). g) The oxidation was performed with $CuCl_2$.

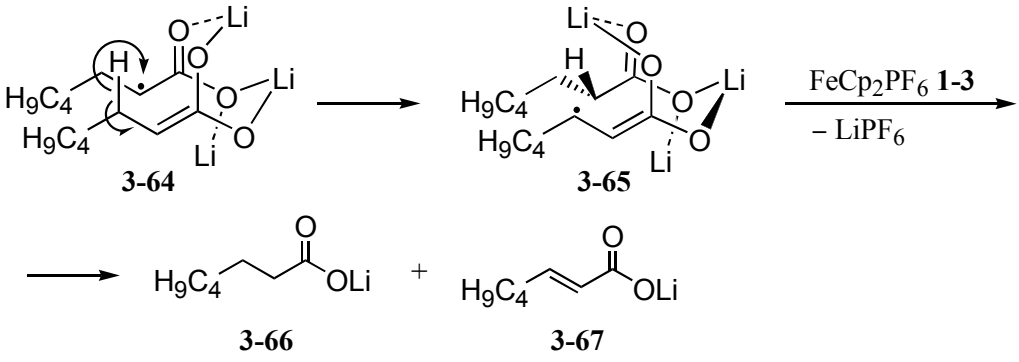
Dimerisation of the enolate of **3-1a** generated by deprotonation with LDA in the presence of 6 equivalents of HMPA gave the dimer **3-3a** in 41% yield with a slight excess of the *d,l*-isomer (Scheme 3.35, Table 3.32, entry 1). The (*Z*)-enolate of *N,N*-diethyl pentanoic amide **3-4d** dimerised with moderate diastereoselectivity (Table 3.32, entries 2-3). The low yields of **3-60** are attributed to the formation of byproducts such as *N,N*-diethyl 2-pentenoic amide **3-61**. In both experiments, some substrate **3-4d** (15-17%) was recovered. Therefore the deprotonation was examined under different conditions. A shorter deprotonation time of 15

min instead of 30 min with larger amounts of LDA afforded **3-60** in only 21% yield (entry 4). Although the amount of recovered **3-4d** was smaller (9%) and *N,N*-diethyl 2-(diisopropylamino)pentanoic amide **3-62** was isolated in 15% yield, and the overall mass balance decreased. In another experiment the amide was deprotonated with 2.3 equiv. LDA for 15 min, followed by 1 equiv. BuLi for 30 min (entry 5). The dimer **3-60** was isolated in only 19% yield, while 12% of amino ester **3-62** was formed. Interestingly, an increased amount of LDA to 2.3 equivalents and 3.3 equivalents afforded **3-60** and **3-62** in similar yields, but the diastereoselectivity of **3-60** increased significantly to 5:1 and 1:0, respectively (entry 4 versus entry 5). Unfortunately, neither the yield of the dimerisation, nor the yield of the potential useful transformation to **3-62d** could be increased.

The enediolate of heptanoic acid **3-6** underwent oxidative dimerisation in 33% yield with a reasonable 4:1 diastereoselectivity (entry 6). The deprotonation of this acid with LDE gave good results in TEMPO trapping experiments. A similar deprotonation could potentially improve the dimerisation yields.

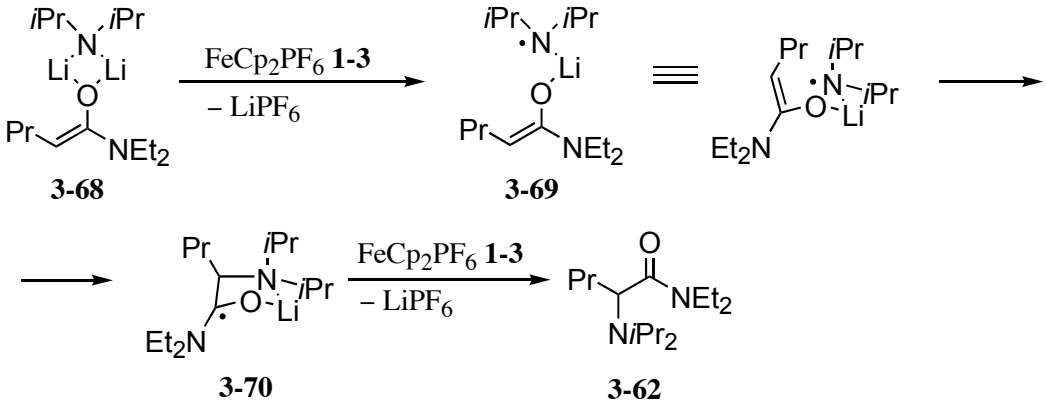
The low yields in dimerisations of amide **3-4d** and acid **3-6** can probably be attributed to a parallel orientation of the α-carbonyl radicals to the enolate units in aggregates like **3-64** (Scheme 3.36). This favours a hydrogen transfer from the enolate unit in a disproportionation reaction or from the solvent re-forming the substrate and the α,β-unsaturated acid or amide.

Scheme 3.36 Formation of product **3-67**



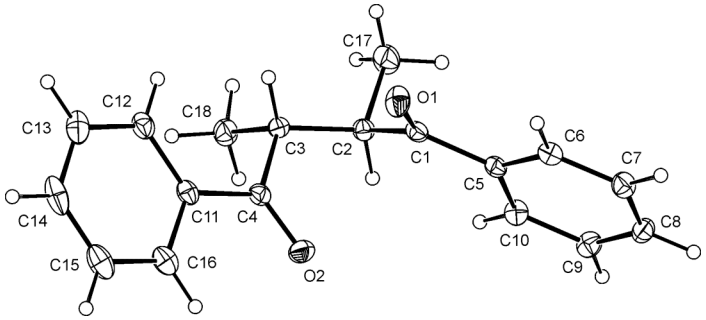
In the reaction of **3-4d** a larger excess of LDA promoted formation of 2-(diisopropylamino)pentanoic amide **3-62**. Formation of mixed aggregates **3-68** containing enolate and LDA units is the likely reason for the surprising formation of **3-62** (Scheme 3.37). Ferrocenium hexafluorophosphate **1-3** oxidised coordinated LDA to a diisopropylaminyl radical **3-69** which added to the neighbouring enolate. The resulting stabilised radical **3-70** is oxidised by another equiv. **1-3** to amino amide **3-62**. Unfortunately the yield of this potentially useful transformation could not be increased.

Scheme 3.37 Formation of product **3-62**



Propiophenone **3-10a** underwent dimerisation in good yields and high *d,l/meso* diastereoselectivity of 10:1 (Table 3.32, entry 7).[25] This reaction proceeded in high yields of 73% and 98% respectively in the presence of LiCl and HMPA (entries 8 and 9). The diastereoselectivity dropped however to 5.5:1 and 4.1:1, respectively. Oxidative coupling with $CuCl_2$ occurred in low yield, but also with diastereoselectivity (entry 10). The major isomer was confirmed to have *d,l*-configuration by its X-ray crystal structure, which shows that the carbon atoms in the α-position of the carbonyl group have opposite configurations (Figure 3.9). The methyl and benzoyl groups are in gauche conformations to each other.

Figure 3.9 X-Ray crystal structure of *d,l*-**3-12a**



Butyrophenone dimerised also in high yields and with high *d,l*-diastereoselectivity (entry 11). The stereochemistry of the dimers was assigned by comparison with **3-12a**.

Substrates with a sterically hindered radical centre like isobutyrophenone **3-10c** or *tert*-butyl ethyl ketone **3-10e** did not dimerise. Octonitrile **3-4b** was also a substrate, which did not undergo oxidative dimerisations. Complex mixtures were isolated.

The resonances of the hydrogen and carbon atoms in the α-carbonyl position are characteristic for dimers **3-12a**, **3-8** and **3-60** (Table 3.33).

Table 3.33 Significant NMR data of dimers **3-12a**, **3-60** and **3-8**

Entry	Dimer	δ (ppm, multiplicity)	
		*CH*CO	CH_2CHCO
1	***d,l*-3-12a**	3.92 (m), 43.5 (d)	-
2	***d,l*-3-60**	2.86 (m), 43.8 (d)	1.56 (m), 33.5 (t)
3	***meso*-3-60**	2.95 (m), 44.9 (d)	1.54 (m), 34.6 (t)
3	***d,l*-3-8**	2.71 (m), 46.0 (d)	1.28-1.62 (m), 31.6 (t)
4	***meso*-3-8**	2.66 (m), 48.0 (d)	1.28-1.62 (m), 31.5 (t)

3.6.3. Influence of the aggregation on the diastereoselectivity

Dimerisations in the presence of substoichiometric amounts of TEMPO

The oxidative heterocouplings with TEMPO and earlier cross-coupling experiments of two different ester enolates[25] indicated that the dimerisations occurred intramolecularly via enolate superstructures. The dynamics of aggregation, i.e. aggregation and deaggregation, may play an important role during dimerisation. It was therefore interesting to find out, to which extent free enolates **3-71** and aggregate-bound enolates **3-72** dimerised (Scheme 3.38). Free radicals **3-73** and aggregate-bound radicals **3-74** should be differentially trapped by TEMPO. It is expected that free radicals **3-73** couple considerably faster with TEMPO than aggregate-bound radicals **3-74**. Therefore, dimerisations of ethyl valerate **3-1a**, *N,N*-diethyl pentanoic amide **3-4d** and cyclohexanone **3-10f** were performed in the presence of substoichiometric amounts of TEMPO.

In a first set of experiments (Method A) defined amounts of 0.1-0.5 equiv. of TEMPO were added to the enolate of ethyl valerate **3-1a** solution before oxidation (Table 3.34). The oxidation was performed by addition of ferrocenium hexafluorophosphate **1-3** in portions at −78 °C over a period of 10 min. To achieve identical conditions, the experiments were performed in parallel. As expected, the yields of the TEMPO adduct **3-2a** increased with higher amount of TEMPO, however, not as much as theoretically expected. The yields of the dimer **3-3a** decreased as expected. The overall mass balance was good to excellent. Compared to the original 2.5:1 *meso/d,l* ratio (see Scheme 3.33), the diastereoselectivities increased in these experiments considerably in a range from 3.1:1 (entry 1) to exceptional 12.6:1 (entry 6). The diastereomeric ratios, obtained in the experiments with 0.3 and especially 0.5 equivalents of TEMPO, were lying outside the trend. These experiments were therefore repeated. Both were not reproduced. While the result in entry 4 did not differ strongly from the experiment in entry 3, the 12.6:1 *meso/d,l*-ratio in entry 6 seems to be an experimental error (compared to

entry 7). These results are nonetheless very positive. The diastereoselectivity was improved significantly to a 3.1-5.4:1 *meso/d,l* ratio. These results support the supposition that TEMPO reacts faster with free α-carbonyl radicals. The aggregate-bound radicals homocoupled more selectively, giving dimers *meso*-**3-3a** in higher excess.

Scheme 3.38 Oxidative coupling of enolates **3-71** in the presence of substoichiometric amounts of TEMPO

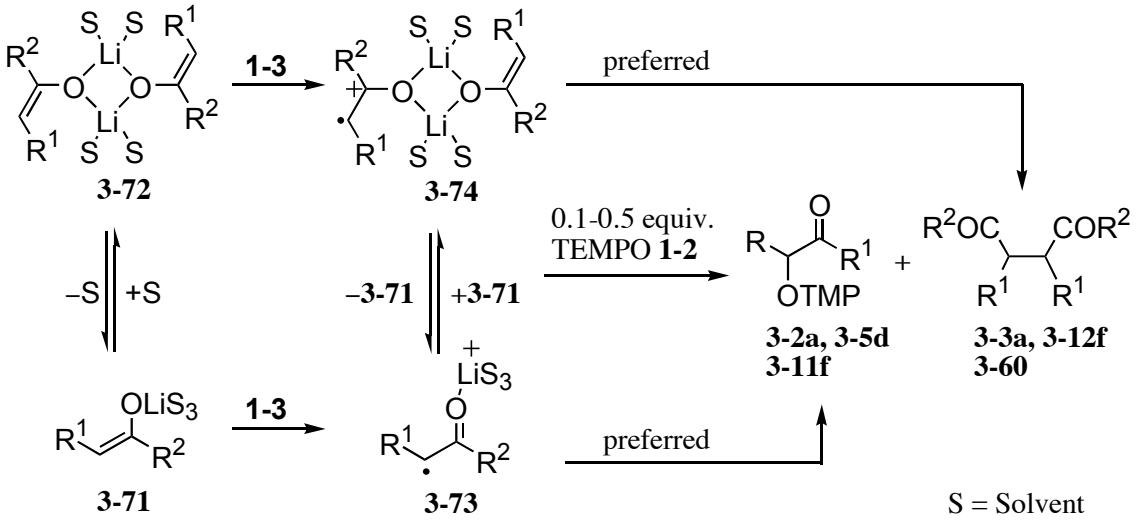


Table 3.34 Dimerisations of ethyl valerate **3-1a** with substoichiometric amounts of TEMPO (Method A: TEMPO **1-2** was added before oxidation with **1-3**)

Entry	Equiv. TEMPO	**3-2a** (%)	**3-3a** (%)	*meso/d,l*
1	0.1	11 (49 mg)	73 (140 mg)	3.1:1
2	0.2	18 (79 mg)	66 (128 mg)	3.6:1
3	0.3	29 (123 mg)	50 (98 mg)	2.6:1
4[a]	0.3	27 (115 mg)	46 (90 mg)	4:1
5	0.4	31 (132 mg)	57 (111 mg)	5.1:1
6	0.5	32 (139 mg)	34 (68 mg)	12.6:1
7[a]	0.5	37 (158 mg)	33 (64 mg)	5.4:1

a) These experiments were repetitions of those in entries 3 and 6 respectively.

In the first set, TEMPO was present from the beginning in the enolate solution and it probably reacted primarily with monomer species. The aggregation dynamics is an equilibrium and it depends on the time and concentration since TEMPO reacted not only with free radicals but also with aggregate bound species. This means that the substoichiometric TEMPO amount was probably consumed before oxidation and dimerisation were finished, since the oxidant was added over a period of ten minutes.

Therefore in a second set of experiments (Method B), TEMPO was homogeneously mixed with ferrocenium hexafluorophosphate and added in portions to the enolate solution (Table 3.35). Compared to method A, the yields of TEMPO adducts **3-2a** were lower (entries 1-5). The dimer **3-3a** was isolated in moderate to good yields of 46-66%. With 0.2 equiv. of TEMPO **1-2** the diastereomeric ratio was with 6.8:1 high (entry 1), while with 0.3 equiv. of TEMPO **1-2** a modest 1.3:1 and 3.6:1 ratio was obtained (entries 2 and 3). Reactions with 0.4 and 0.5 equivalents of **1-2** gave similar diastereoselectivities as method A. The diastereomeric ratio was with 5.0-5.4:1 good. A significant improvement of diastereoselectivity was achieved also in this case.

Table 3.35 Dimerisations of ethyl valerate **3-1a** with substoichiometric amounts of TEMPO[a]

Entry	Equiv. TEMPO	**3-2a** (%)	**3-3a** (%)	*meso/d,l*
1	0.2	11 (48 mg)	53 (103 mg)	6.8:1
2	0.3	14 (61 mg)	46 (89 mg)	1.3:1
3[b]	0.3	16 (69 mg)	51 (108 mg)	3.6:1
4	0.4	14 (62 mg)	66 (129 mg)	5.4:1
5	0.5	7 (29 mg)	51 (82 mg)	5.0:1
6[b]	0.5	32 (92 mg)	48 (93 mg)	5.2:1

a) Method B: TEMPO **1-2** was homogeneously mixed with **1-3**. b) These experiments were a repetition of the experiments in entries 2 and 5, respectively.

In a third set of experiments, 0.1 equivalents of TEMPO were added prior to oxidation (Table 3.36). The remaining TEMPO was homogeneously mixed with ferrocenium hexafluorophosphate **1-3** and added in portions (Method C). The TEMPO adduct **3-2a** was isolated in 19-28% yields, while the dimer **3-3a** was obtained in good yields of 56-69%. The diastereoselectivity was better than in the absence of **1-2** (compared to scheme 3.32) and relatively constant in the range 3.0-3.7:1 for all experiments.

Table 3.36 Dimerisations of **3-1a** with substoichiometric amounts of TEMPO[a]

Entry	Equiv. **1-2**	**3-2a** (%)	**3-3a** (%)	**3-3a** *meso/d,l*
1	0.2	19 (80 mg)	66 (128 mg)	3.3:1
2	0.3	22 (93 mg)	69 (133 mg)	3.7:1
3	0.4	21 (88 mg)	65 (126 mg)	3.6:1
4	0.5	28 (119 mg)	56 (108 mg)	3.0:1

a) Method C: 0.1 equiv. of TEMPO **1-2** was added before oxidation; the remaining amount was homogeneously mixed with ferrocenium hexafluorophosphate **1-3**.

The presence of a persistent radical (TEMPO) in substoichiometric amounts in the enolate solution during the oxidation consumed a part of the free radicals present in solution and allowed the dimerisation in aggregates to a larger extent. The diastereoselectivity of oxidative dimerisations was improved significantly. The deaggregation of **3-72** to **3-71** is possible, while the deaggregation of the radical anion **3-74** to radical **3-73** and enolate **3-71** is rather unlikely as earlier computational calculations have shown.[118] All three methods with substoichiometric amounts of TEMPO showed a similar trend of increasing diastereoselectivity. The results were, however, different since the initial concentration and the concentration profile of TEMPO throughout the reaction influenced the reaction significantly. Qualitatively it seems logic why rather constant diastereoselectivity is observed with method C, since TEMPO traps free radicals constantly. In method A and though less also in method B TEMPO is consumed competitively - fast by free radicals and slower by aggregate-bound radicals. The lower the TEMPO concentration in the beginning the faster it is consumed and for the most part of the reaction TEMPO is not present. The higher the initial concentration, the longer the trapping can last increasing the diastereoselectivity. These results indicate that aggregation plays an important role in this reaction. Further investigations must prove this hypothesis.

Dimerisation of cyclohexanone **3-10f** according to method A afforded the dimer **3-12f** in a moderate yield of 41%, while the diastereoselectivity did not change significantly (Table 3.37, entry 1). Dimerisations of *N,N*-diethyl pentanoic amide **3-4d** according to methods A and B gave dimers **3-60** in very low yields, but with complete *d,l*-selectivity (entries 2 and 3).

Table 3.37 Dimerisations in the presence of 0.3 equiv. TEMPO **1-2**

Entry	Substrate	Enolate config.	Method	**3-11f** or **3-5d** (%)	dimer (%)	*d,l/meso*	*d,l/meso* without **1-2**
1	**3-10f**	*E*	A	**3-11f** 24	**3-12f** 41	1:1.3	1.1:1[c]
2[a]	**3-4d**	*Z*	A	**3-5d** 30	**3-60** 11	*d,l*	2.5:1[d]
3[b]	**3-4d**	*Z*	B	**3-5d** 21	**3-60** 16	*d,l*	2.5:1[d]

a) 2% of **3-61** and 19% of **3-4d** were isolated. b) 8% of **3-61**, 6% of **3-62** and 20% **3-4d** were isolated. c) See Table 3.30, entry 1. d) See Table 3.32, entry 2.

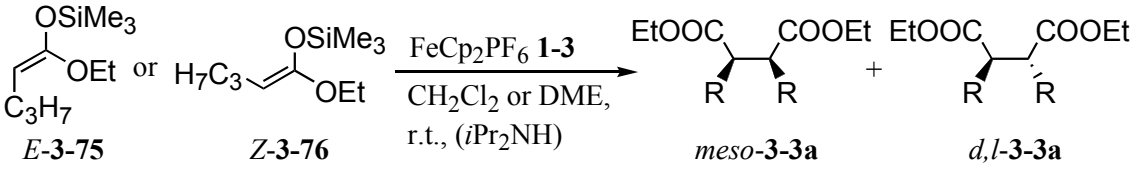
3.6.4 Dimerisations of silyl ketene acetals

To gain more information on the importance of enolate geometry, dimerisations of enolates with "fixed" geometry in the form of the (*E*)-silyl ketene acetals or (*Z*)-silyl ketene acetals of **3-1a**, were investigated (Scheme 3.39). An interesting feature was to examine the

role of diisopropylamine from LDA. The (*E*)-silyl ketene acetal ***E*-3-75** and (*Z*)-silyl ketene acetal ***Z*-3-76** of ethyl valerate were synthesised using adapted literature procedures in ratios 4-7:1.[119]

Since the oxidation potential of ***E*-3-75** is higher than that of the corresponding lithium enolate,[120] the oxidation times (2.5-36 h) were much longer, but the dimerisation of (*E*)-silyl ketene acetal ***E*-3-75** in the presence or absence of *i*Pr_2NH remained inefficient giving the dimer **3-3a** in low yields of 10-28% (Table 3.38). The diastereoselectivities were also low.

Scheme 3.39 Dimerisation of silyl ketene acetals



E-**3-75** *Z*-**3-76** *meso*-**3-3a** *d,l*-**3-3a**

Table 3.38 Dimerisation of (*E*)-silyl ketene acetal ***E*-3-75**

Entry	(*E/Z*)-ratio[a]	Additives (equiv.)	Time (h)	**3-3a** (%)	*meso/d,l*
1[a]	4:1	*i*Pr_2NH (1.0)	2.5	10	-
2[a]	4:1	-	10.5	28	1.3:1
3[b]	6.4:1	-	36	15	1.2:1

a) 0.3*M* in CH_2Cl_2. b) 0.3*M* in DME.

The dimer **3-3a** was obtained in low to moderate yields of 15-56% when ***E*-3-75** or ***Z*-3-76** was transmetallated with MeLi to the amine-free (*E*)-enolate ***E*-3-77** or (*Z*)-enolate ***Z*-3-78** (Scheme 3.40, Table 3.39, entries 1-8). Long transmetallation times (90 min) at higher temperatures of −30 to 20 °C triggered anionic competing processes leading to the formation of trimer **3-34a** in yields from 10 to 30%. Enolate ***E*-3-77** gave *meso*-**3-3a** preferentially, but only in a slight excess (entries 1, 2, 4 and 5) while ***Z*-3-78** furnished **3-3a** with a slight excess of the *d,l*-diastereomer (entry 8). Generally the obtained diastereoselectivities were very low and also not reproducible. A significant influence of the ***E*-3-77**:***Z*-3-78** ratio on the reaction outcome could not be established. The *meso/d,l* ratios did not reflect the initial *E:Z* enolate ratio, therefore a clear correlation between the (*E/Z*)-geometry of the enolate and diastereoselectivity of dimerisations was not established from these experiments. The oxidation of the lithium enolates ***E*-3-77** or ***Z*-3-78** prepared from ***E*-3-75** or ***Z*-3-76** in the presence of *i*Pr_2NH induced neither significant changes nor reproducible diastereoselectivities (entries 9-11). Experiments in the presence of substoichiometric amounts of TEMPO afforded

low yields of **3-3a** with variable diastereoselectivities (entries 12-14). Consequently no new information or mechanistic insights on correlation between (*E/Z*)-enolate geometry and diastereoselectivity was gathered from these experiments.

Scheme 3.40 Transmetallation of silyl ketene acetals with MeLi and their oxidative dimerisation

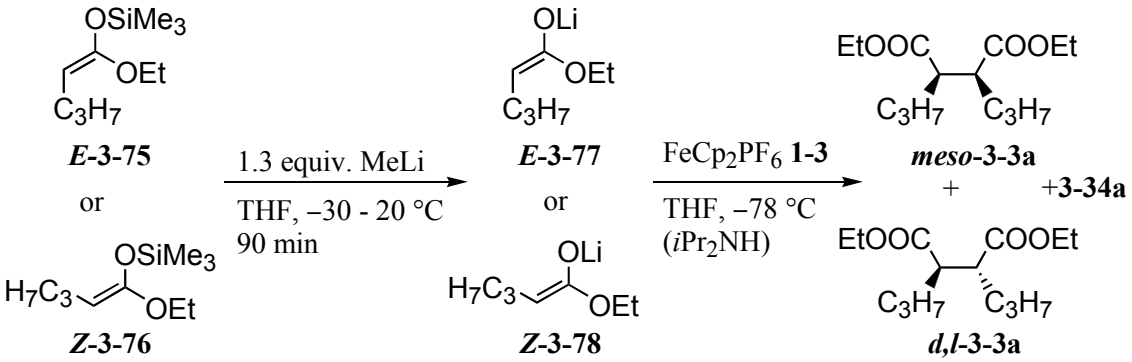


Table 3.39 Dimerisation of (*E*)- and (*Z*)-silyl ketene acetals ***E*-3-75** and ***Z*-3-76**

Entry[a]	*E:Z*	Additives (equiv.)	**3-2a** (%)	**3-3a** (%)	*meso/d,l*	**3-34a** (%)
1[b]	4:1	-	-	56	1.8:1	10
2[c]	6.4:1	-	-	23	1.9:1	29
3[c]	4.5:1	-	-	43	1:1.2	30
4	4.5:1	-	-	40	1.5:1	26
5	7:1	-	-	45	1.6:1	28
6	7:1	-	-	15	1:1	26
7[d]	1:7	-	-	31	-	-
8[e]	1:7	-	-	56	1:1.4	16
9	5.5:1	*i*Pr$_2$NH (1.3)	-	58	3.2:1	20
10	7:1	*i*Pr$_2$NH (1.3)	-	50	1.1:1	22
11	6.7:1	*i*Pr$_2$NH (1.3)	-	41	1:1	41
12	4.5:1	TEMPO (0.3)	27	16	4.6:1	32
13	7:1	TEMPO (0.3)	27	29	1.3:1	12
14	6.7:1	TEMPO (0.3)	30	5	1:0	52

a) Unless otherwise specified, the general conditions were: Transmetallation with 1.3 equiv. of MeLi at –30 °C for 5 min and at r.t. for 90 min in 0.1*M* solution of the substrate in THF; oxidation with 1-2 equiv. of **1-3** at –78 °C for 15-30 min. b) 1 equiv. MeLi. c) 1.15equiv. MeLi. d) Transmetallation at –30 - –15 °C for 40 min. e) Transmetallation at –40 - –30 °C for 30 min.

3.7. Mechanistic rationalisation of oxidative coupling reactions of enolates

The α-oxygenation of carbonyl compounds via SET oxidation of their enolates to an α-carbonyl radical induced by ferrocenium hexafluorophosphate **1-3**, followed by trapping with TEMPO **1-2** is generally applicable. All substrates gave the α-oxygenated carbonyl compounds in high yields, with the exception of α,α-dialkyl amides and ketones. Carbonyl compounds bearing adjacent chiral centres react with low to moderate diastereoselectivities. The oxygenation of ester **3-1b** occurs probably via trapping of the chelated alkoxide radical **A** (Figure 3.10). The approach of TEMPO takes place at the β-face affording the *anti*-isomer, similarly to the Frater-Seebach alkylation.[121] However, the more hindered α-face is also accessible for radical trapping leading to relatively low *anti/syn* selectivity. Unexpectedly, steric effects do not play a role in the radical oxygenation of (*R*)-camphor **3-10h**. **1-2** couples with the α-carbonyl radical equally from both faces, although the *exo*-face is more hindered. Similarly ethyl (*S*)-2-pyrrolidone-5-carboxylate **3-4i** gives a low diastereoselectivity. This speaks for an early transition state of the radical coupling.

Figure 3.10 Radical coupling of **3-1b** with TEMPO

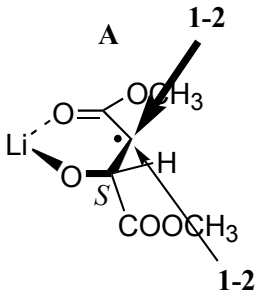
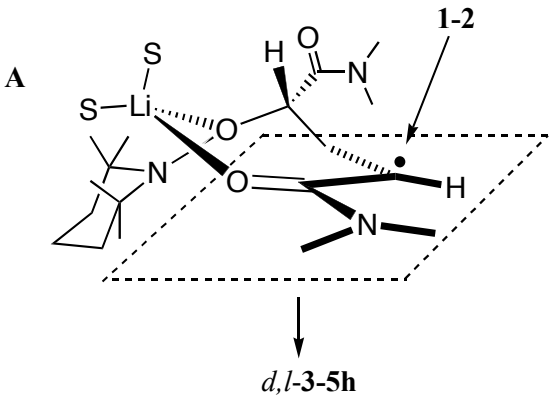


Figure 3.11 Model for the preferred formation of *d,l*-**3-5h**



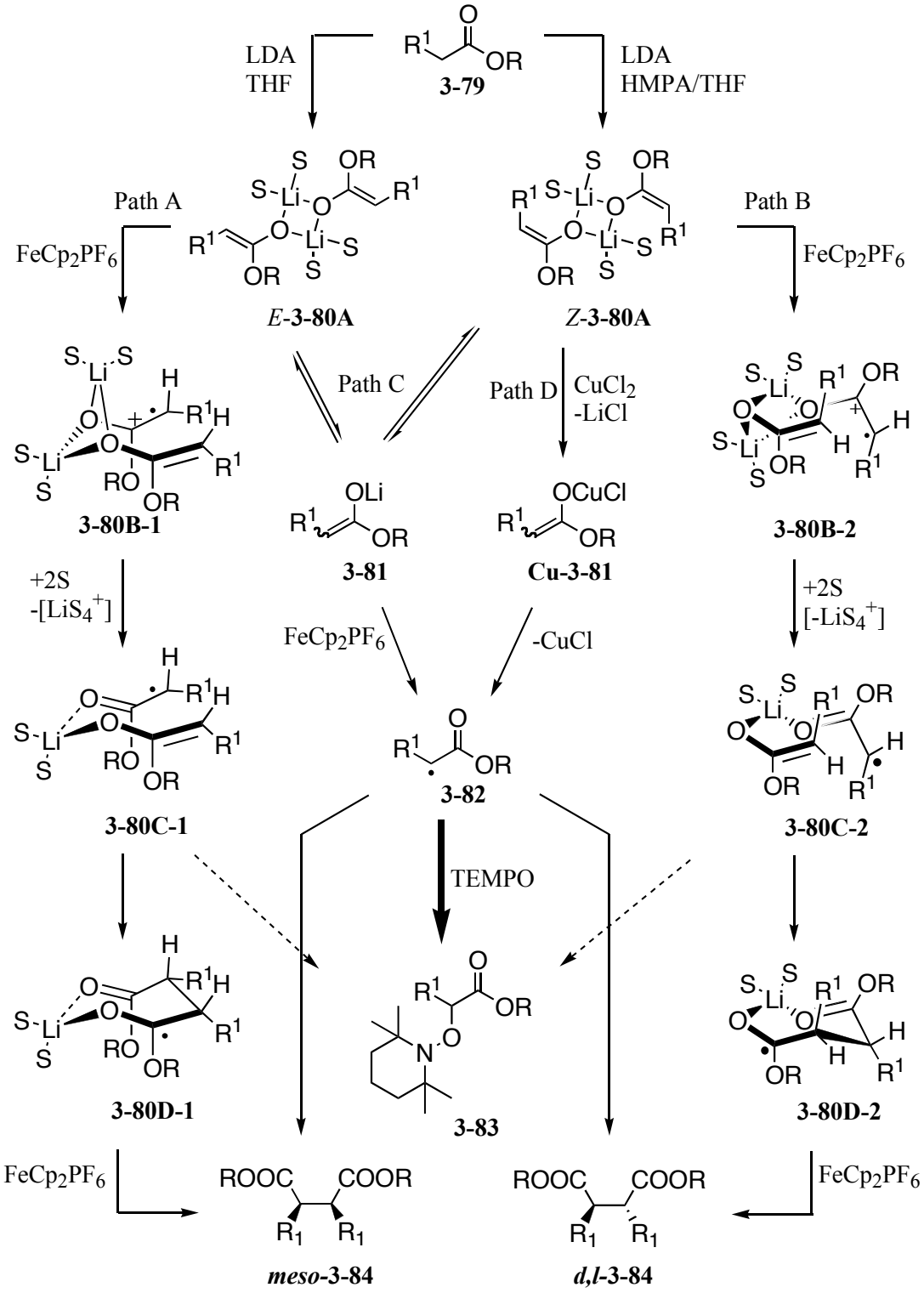
The diastereoselectivity of radical coupling with glutaric diamide **3-4h** can be rationalised by assuming that the α-carbonyl radical of amide **3-4h** has to be flat and in the same plane with the neighbouring amide group (Figure 3.11). Considering a 7-membered ring chelated transition state like **A**, TEMPO **1-2** approaches from the β-face forming *d,l*-**3-5h** in excess. The residing tetramethylpiperidin-1-yl unit apparently blocks the α-face relatively efficiently. The minor isomer may result from an open transition state.

Unhindered aliphatic esters, carboxylic acids, aromatic ketones and in part amides form unexpectedly large amounts of dimers via homocoupling of the α-carbonyl radicals. Oxidative dimerisations compete, although TEMPO trapping with α-carbonyl radicals is a very fast process ($k = 10^7$-10^9 $M^{-1}s^{-1}$).[122] Moreover, the persistent radical effect of TEMPO should inhibit the homocoupling of transient α-carbonyl radicals **3-82** (Scheme 3.41). The surprising formation of dimers is ascribed to the aggregation effects of enolate solutions.[25] As most other organolithium compounds, the enolates of esters and amides aggregate as dimers, while ketone enolates assemble in tetrameric superstructures.[1, 81] Different degrees of diastereoselectivity in dimerisations of esters, amides and ketones, respectively, reflect that, while classical radical homocouplings should take place without diastereoselectivity. Diastereoselective radical dimerisations were reported rarely, usually for chiral auxiliaries bound radicals.[62,70]

The diastereoselectivity seems to be correlated to some extent with the enolate geometry. It was observed that acyclic (*E*)-enolates form preferentially *meso*-dimers, while (*Z*)-enolates give an excess of *d,l*-isomers. Yet the *meso:d,l* ratio of dimers does not reflect the selectivity of enolate formation. Hence the diastereoselectivity of dimerisation must be a result of combined aggregation effects and enolate geometry.

Ester **3-79** is deprotonated to aggregate *E*-**3-80A** in THF (Scheme 3.41, path A). Single electron oxidation with ferrocenium hexafluorophosphate leads to formation of radical cation **3-80B-1**. Elimination of tetracoordinated Li^+ generates radical **3-80C-1**, composed of an α-carbonyl radical unit **3-82** and an enolate unit *E*-**3-81**. **3-80C-1** undergoes a 7-*endo* cyclisation to radical **3-80D-1** through a radical addition of the α-carbonyl radical to the enolate unit with preferential *meso*-diastereoselectivity. This is the key step, which determines the diastereoselectivity of the products. Another SET step gives dimer *meso*-**3-84**. Structures like **3-80B-1**, **3-80C-1**, and **3-80D-1** were approximated by DFT calculations for methyl propionate in Me_2O.[118] The calculations supported the theory that formation of *meso*-dimer from the (*E*)-enolate is energetically favoured for this case.

Scheme 3.41 Rationalisation of the dimerisation diastereoselectivity of esters and amides



In THF/HMPA the (*Z*)-enolate aggregates to *Z*-**3-80A** (Path B). SET oxidation by ferrocenium hexafluorophosphate gives **3-80B-2**, which forms radical **3-80C-2** by elimination of a lithium cation. 7-*endo*-Cyclisation to **3-80D-2** followed by SET oxidation affords *d,l*-**3-84**. Similarly, amide enolates, which have a (*Z*)-geometry, form the *d,l*-isomer with high selectivity. Monomeric enolates **3-81** are in equilibrium with *E*-**3-80A** or *Z*-**3-80A** (Path C).

They are oxidised to free radicals **3-82**, which undergo unselective radical homocoupling to both *meso*- and *d,l*-**3-84**. The investigations on the role of aggregates and enolate geometry can be outlined as follows:

1) Hartmann performed crossover oxidative dimerisations of ethyl butyrate and ethyl valerate with different mixing time of their enolate solutions.[25] The ratio of formed homodimers and heterodimers and the constant diastereoselectivity of 2:1 *meso*:*d,l* for all formed dimers substantiated that aggregation plays an important role in the mechanism of this reaction.

2) The addition of the oxidant has an impact on diastereoselectivity. Addition of the oxidant at once to the enolate solution of ethyl valerate gave a 1.5:1 *meso:d,l* ratio, while addition in portions gave a 2.5:1 ratio (Scheme 3.33). Addition at once generates a high concentration of α-carbonyl radicals, and the dimerisation occurs mostly via radical coupling. When the oxidant is added in portions, a small concentration of α-carbonyl radicals is generated stepwise and the radical addition to the enolate units inside of an aggregate dimer like **3-80C-1** and **3-80C-2** prevails.

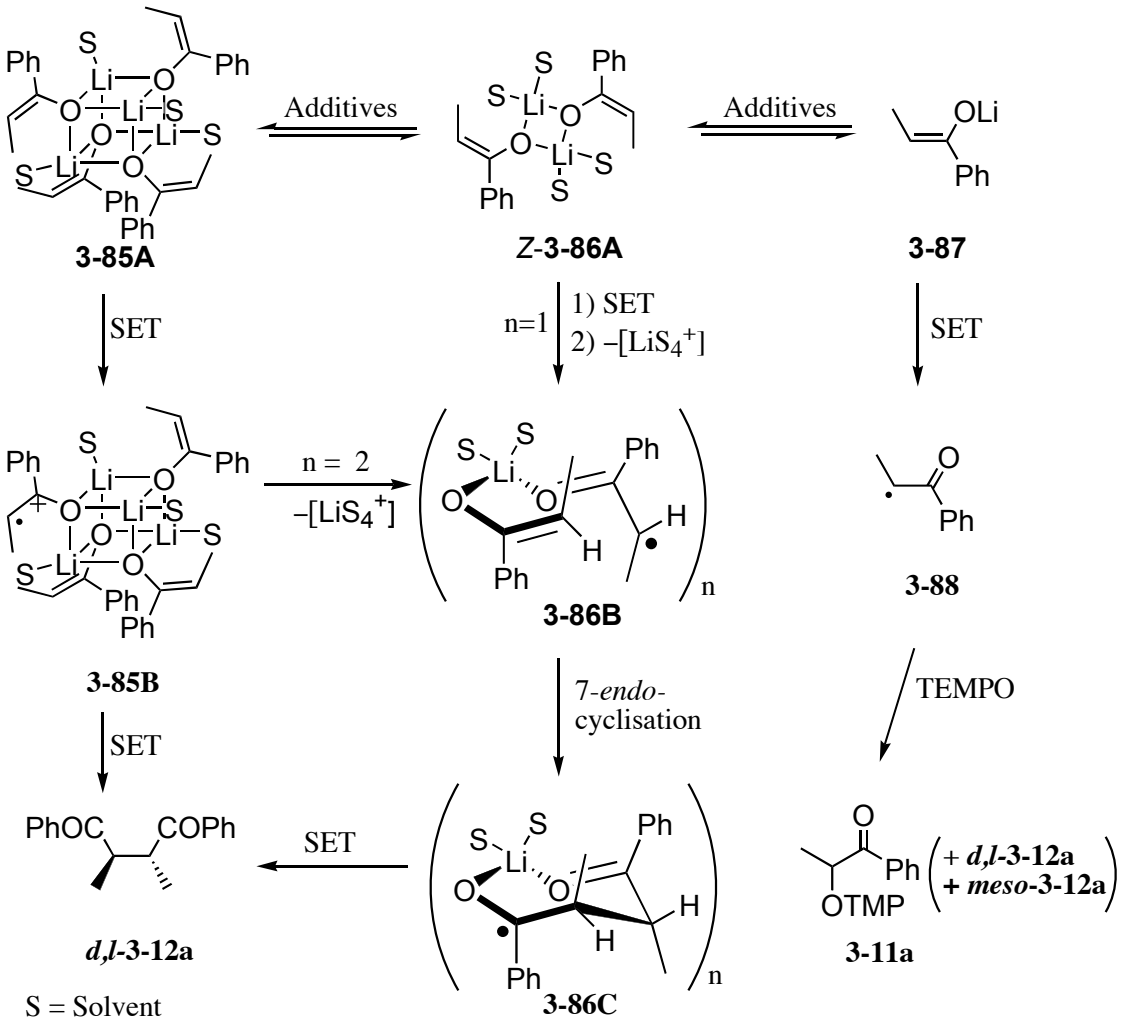
3) The dimerisation experiments with substoichiometric amounts of TEMPO improved the diastereoselectivity of *meso*-**3-3a** significantly (Tables 3.34, 3.35 and 3.36). TEMPO traps preferentially the free α-carbonyl radicals **3-82** giving product **3-83**. These results support the theory that aggregation induces diastereoselectivity. The bound α-carbonyl radicals in **3-80C-1** undergo a radical addition to the neighbouring enolate unit, leading to *meso*-**3-3a**. The α-carbonyl radical features a high rotation barrier, and therefore its partial allylic character makes a conformational rotation slow.[123] In this way the orientation of substituents in the enolate will be retained in the α-carbonyl radical. The facts speak for the retention of the enolate configuration in the conformation of the radical.

4) The diastereoselectivity of dimerisation does not reflect the selectivity of enolate formation. The preparation of silyl ketene acetals via quenching of the enolate with TMSCl allows the accurate determination of the (*E*/*Z*)-enolate ratio present in solution (see Tables 3.38 and 3.39). This ratio can be variable. Their transmetallation with MeLi generates the corresponding lithium enolate with retention of the (*E*/*Z*)-ratio, allowing in principle the investigation of the correlation between the (*E*/*Z*)-enolate ratio and the *meso*/*d,l*-dimer ratio, in the absence of *i*Pr_2NH, HMPA or other lithium-coordinating agents. Unfortunately, the dimerisation experiments of silyl ketene acetals provided inconsistent results.

5) The nature of the oxidant and the mechanism of oxidation play also an important role. The *meso*:*d,l* dimer ratio amounted to 2.5:1 with ferrocenium hexafluorophosphate,

which is an outer sphere oxidant (Scheme 3.33). In contrast no diastereoselectivity was observed with $CuCl_2$, which is an inner sphere oxidant.[25] $CuCl_2$ transmetallates Li^+ in ***E*-3-80A** or ***Z*-3-80A**, giving covalent copper enolate **Cu-3-81** (Scheme 3.41, path D). Inner sphere oxidation forms a free α-carbonyl radical **3-82**, which couples unselectively to both *meso*-**3-84** and *d,l*-**3-84**.

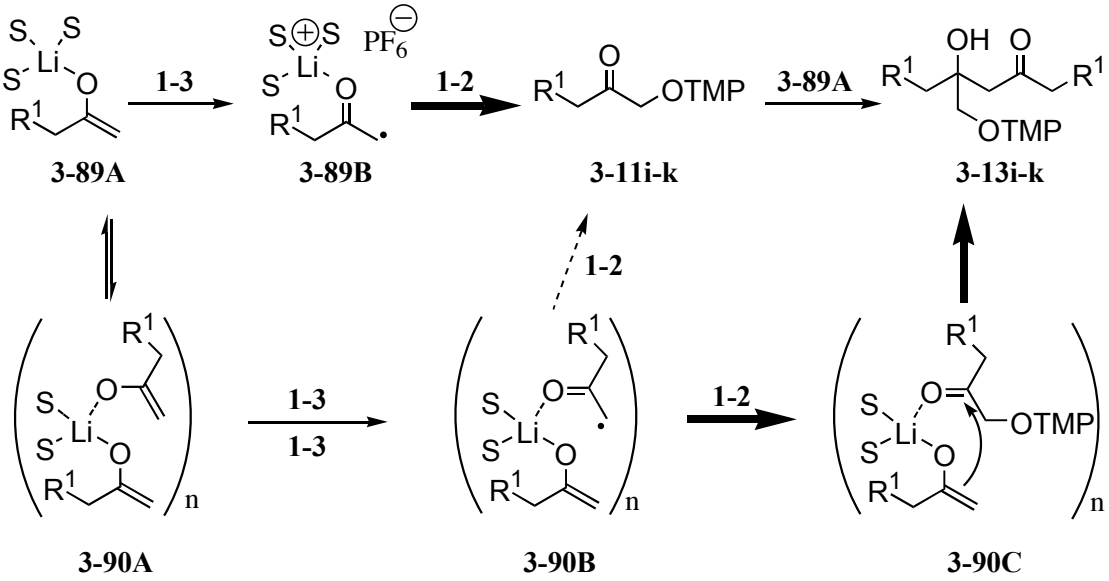
Scheme 3.42 Dimerisation of propiophenone



Similar arguments explain the highly selective formation of *d,l*-**3-12a** (Scheme 3.42). Propiophenone enolates aggregate in tetrameric superstructures like **3-85A**. The addition of **1-3** in portions oxidises the enolate to an α-carbonyl radical, which is surrounded by three enolate units in aggregates like **3-85B**. Radical addition to a neighbouring unit followed by a second oxidation gives *d,l*-**3-12a**. In competition dissociation generates **3-86A** whose oxidation leads via **3-86B** to radical **3-86C**, which is further oxidised to *d,l*-**3-12a**. The concentration of monomer **3-87** gives both dimers *d,l*-**3-12a** and *meso*-**3-12a** unselectively. Aggregate-bound radicals preferentially undergo radical addition to a neighbouring enolate

unit. This explains the high yield of the dimer *d,l*-**3-12a** formed in the presence of TEMPO (Scheme 3.5, table 3.7, entry 1). In the presence of lithium-coordinating additives like HMPA or aggregate-breaking additives like LiCl, the concentration of free enolate units **3-87** increases giving more of **3-11a**.

Scheme 3.43 Formation of main products in the α-oxygenation of methyl ketones **3-10i-k**

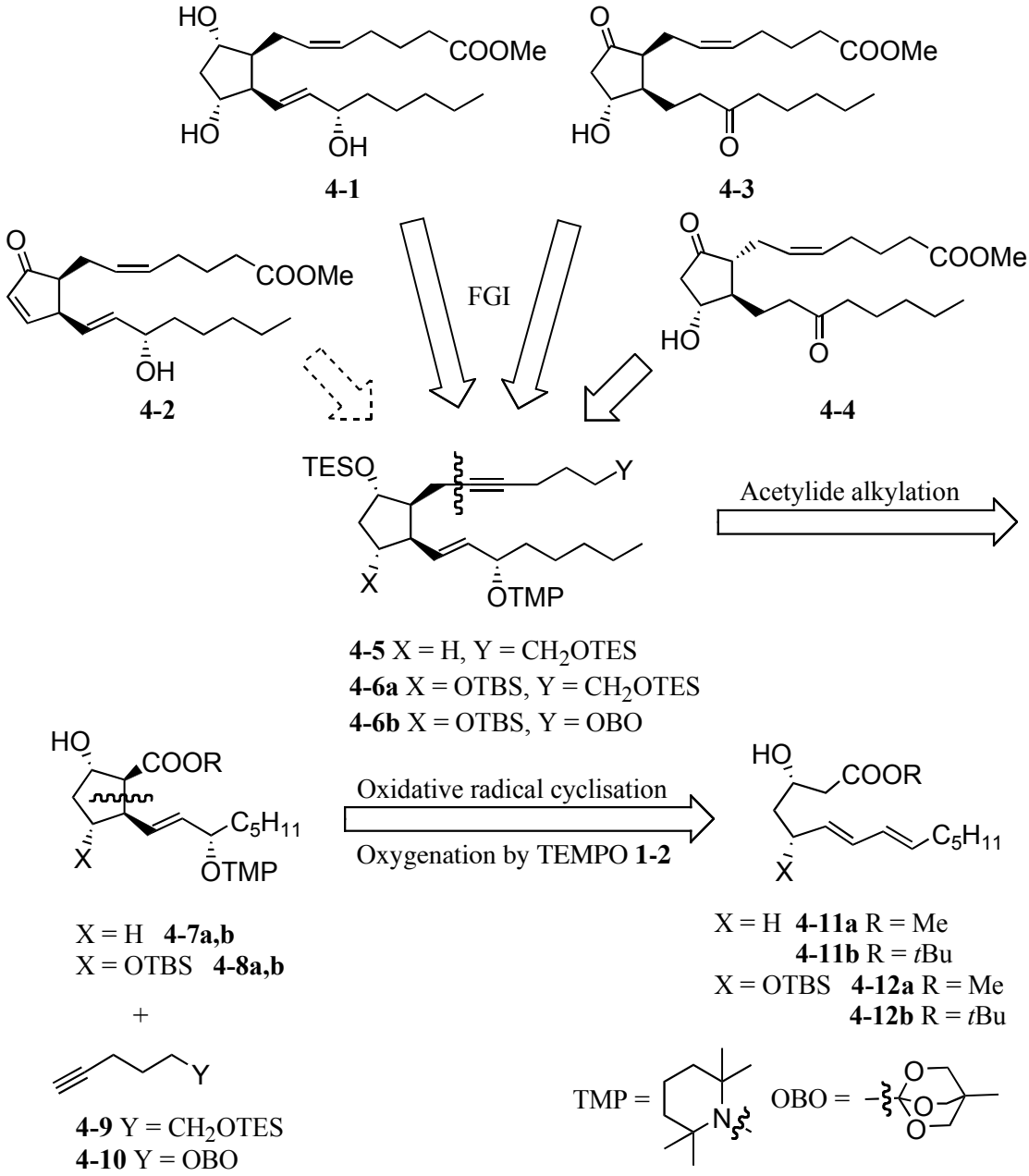


Methyl ketones **3-10i-k** were deprotonated kinetically and oxygenated with high regioselectivity at the methyl position. Nonetheless a number of byproducts were isolated. The enolate **3-89A** is in equilibrium with the aggregate **3-90A** (Scheme 3.43). SET oxidation of **3-89A** to **3-89B** and trapping by **1-2** gives product **3-11i-k**. SET oxidation of **3-90A** forms the aggregate bound radical **3-90B**, which couples with **1-2** affording intermediate **3-90C**. Formation of **3-90C** is possible because **1-3** is added in portions and a small amount of α-carbonyl radicals is generated at a time. An aldol addition of the enolate to the trapping product follows giving hydroxy ketone **3-13i-k**. Small amounts of byproducts resulting from the internal deprotonation of methyl ketones **3-10i-k** were also observed. They form by similar pathways. Addition of the oxidant **1-3** at once would generate a high concentration of α-carbonyl radicals, which may be trapped by **1-2** and increase the yield of **3-11i-k**. Dimers resulting from homocoupling, which were isolated in small amounts, may also form in higher yields.

4. Oxidative radical cyclisations of enolates and application to new efficient total syntheses of 15-F_{2t}-isoprostane, 13,14-dihydro-15-oxo-E_2-isoprostane and 13,14-dihydro-15-oxoprostaglandin E_2

4.1. Retrosynthesis

Scheme 4.1 Retrosynthetic disconnection of **4-1**, **4-2** and **4-3**



This chapter presents the development of an oxidative cyclisation method and its application to the total synthesis of the methyl ester of racemic 15-F_{2t}-IsoP **4-1**. Moreover the complete carbon skeleton of 15-A_2-IsoP **4-2** was assembled. This method was also applied to

the total synthesis of potential metabolites of 15-E_2-IsoP **1-55**, namely the racemates of 13,14-dihydro-15-oxo-E_2-IsoP **1-59** and 13,14-dihydro-15-oxo-PG E_2 **1-60** in the form of their methyl esters **4-3** and **4-4**.

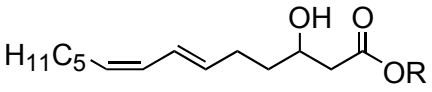
The retrosynthetic analysis of 15-F_{2t}-IsoP methyl ester **4-1**, 15-A_2-IsoP methyl ester **4-2** and 13,14-dihydro-15-oxo-15-E_2-IsoP methyl ester **4-3** calls for the crucial C-C bond forming steps early in the synthetic strategy and an adjustment of the functional groups in derivatives **4-5** and **4-6** in the final part of the synthesis (Scheme 4.1). The disconnection of the C6-C7 bond leads to derivatives of hex-5-ynoate **4-9** or **4-10** and hydroxycyclopentanecarboxylates **4-7a,b** or **4-8a,b**. This disconnection is new in isoprostane chemistry. The cyclopentane ring systems **4-7a,b** and **4-8a,b** will be approached by oxidative radical 5-*exo*-cyclisations of 3-alkoxido enolates of **4-11a,b** and **4-12a,b** respectively. The oxygen functionality in the 15-position will be introduced using TEMPO **1-2**.[124]

4.2. Synthesis of starting materials for the oxidative radical cyclisations

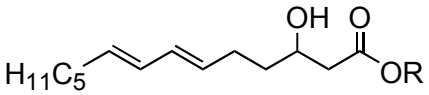
4.2.1. Cyclisation precursors for 15-A_2-IsoP 4-2

The impact of different structural features like ester size and geometry of the double bond on the radical cyclisation outcome had to be studied in the course of the total synthesis. Therefore two isomeric pairs of compounds **4-11** were synthesised (Figure 4.1).

Figure 4.1 Cyclisation precursors for A_2-isoprostane synthesis



(6E,8Z)-**4-11a** R = Me
(6E,8Z)-**4-11b** R = *t*Bu



(6E,8E)-**4-11a** R = Me
(6E,8E)-**4-11b** R = *t*Bu

*4.2.1.1. An efficient synthesis of 15-A_2-IsoP precursors (6E,8Z)-**4-11a** and (6E,8E)-**4-11a,b***

Radical isomerisation of the (*Z*)-double bond of commercially available *(2E,4Z)*-ethyl 2,4-decadienoate *(2E,4Z)*-**4-13** gave *(2E,4E)*-**4-14** in 88% yield by irradiation in benzene in the presence of catalytic amounts of Ph_2S_2 for 4 h (Scheme 4.2). Subsequent reduction of *(2E,4E)*-**4-14** with DIBAL-H afforded dienol *(2E,4E)*-**4-15** in an excellent 94% yield.[125] The double bond geometry ratios *(2E,4E)*-**4-15**:*(2E,4Z)*-**4-15** varied in the range 6-14:1. The reduction of ester *(2E,4Z)*-**4-14** was conducted with $LiAlH_4$, affording dienol *(2E,4Z)*-**4-15** in 75 and 71% yields respectively.[126] Small amounts of dienol *(2E,4E)*-**4-15** were often observed in the NMR spectra.

Scheme 4.2 Synthesis of bromide *(2E,4E)*-**4-16**

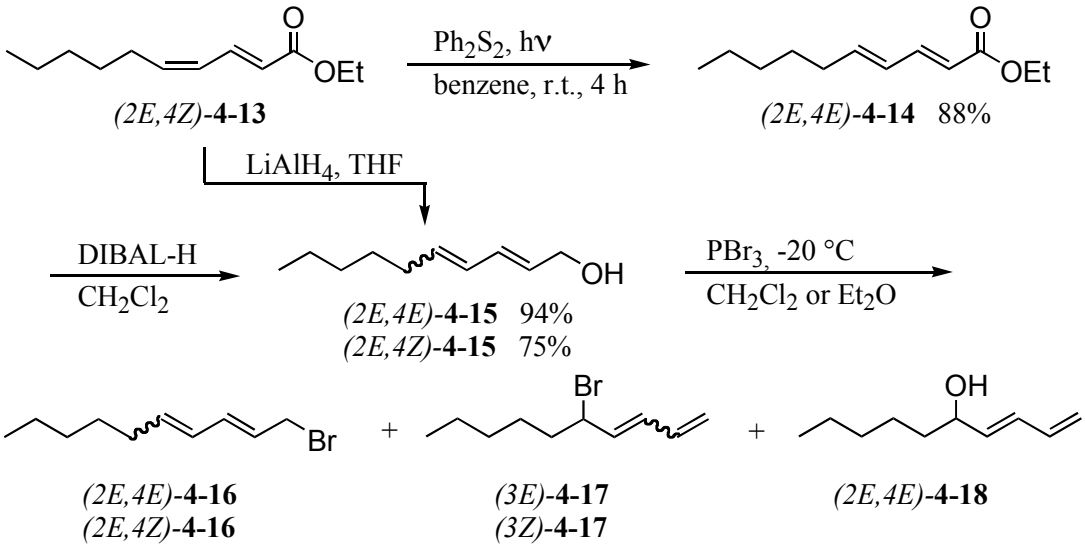


Table 4.1 Bromination experiments of *(2E,4Z)*-**4-15** and *(2E,4E)*-**4-15**

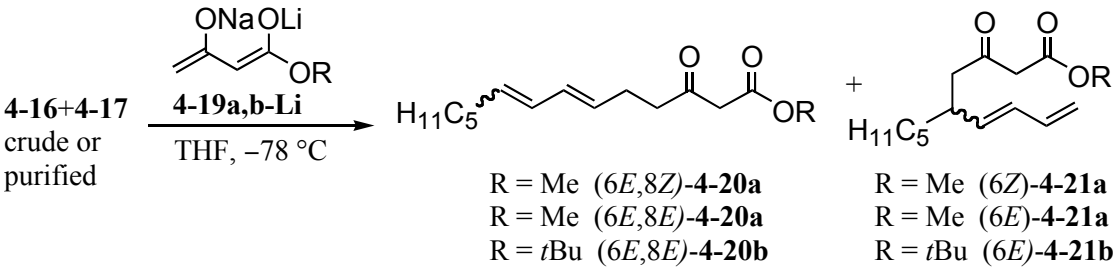
Entry	Substrate	Bromide	Solvent	Product distribution **4-16**: **4-17**: **4-18**	Yield (%)[a] **4-16**+**4-17**+**4-18**
1	*(2E,4Z)*-**4-15**	*(2E,4Z)*-**4-16**	Et_2O	3.4:1:0	61%[b]
2	*(2E,4E)*-**4-15**	*(2E,4E)*-**4-16**	Et_2O	3.8:1:0	90%[c]
3	*(2E,4E)*-**4-15**	*(2E,4E)*-**4-16**	CH_2Cl_2	4.3:1:1.8	99%[d]
4	*(2E,4E)*-**4-15**	*(2E,4E)*-**4-16**	CH_2Cl_2	1.7:1:0 crude	90%
				8.7:1:2.6 purified	85%[e]

a) Determined from the ^{1}H NMR spectrum of the crude product. b) Detectable amounts of *(2E,4E)*-**4-16** and of a third isomer, which is probably *(2Z,4E)*-**4-16** (doublet at 4.12 ppm, J = 8.8 Hz, q at 2.37 ppm, J = 13.4, 6.7 Hz) were observed in the ^{1}H NMR spectrum. c) *(2E,4E)*-**4-16:***(2E,4Z)*-**4-16** 10:1. d) *(2E,4E)*-**4-16:***(2E,4Z)*-**4-16** 9:1. e) Isolated yield of products after flash chromatography; *(2E,4E)*-**4-16:***(2E,4Z)*-**4-16** 18:1.

The conversion of **4-15** to bromide **4-16** represented a challenge (Scheme 4.2). The bromination with Br_2/Ph_3P or CBr_4/Ph_3P afforded complex mixtures containing large amounts of Ph_3P=O, although the preparation with Br_2 was previously reported.[125b, 127] Purification of the very labile bromide by kugelrohr distillation allowed separation from Ph_3P=O, but the mass balance was low due to thermal decomposition and the bromide was obtained as a component of a complex mixture. In contrast, the bromination with PBr_3[125c, 128] furnished a mixture of the labile desired terminal bromide **4-16** and undesired internal bromide **4-17** in ratios of 1.7-4.3:1 (Table 4.1).

The formation of terminal bromides **4-16** was favoured in dry diethyl ether in a ratio of *(2E,4Z)*-**4-16**:*(3Z)*-**4-17** 3.4:1 and *(2E,4E)*-**4-16**:*(3E)*-**4-17** 3.8:1, respectively (Entries 1 and 2). A different outcome was observed in the bromination in dry CH_2Cl_2. The internal bromide *(3E)*-**4-17** was partially hydrolysed during workup to the internal dienol *(3E)*-**4-18** (entry 3). The ratio of *(2E,4E)*-**4-16**:*(3E)*-**4-17**:*(3E)*-**4-18** was determined to 4.3:1:1.8 by ^{1}H NMR spectroscopy, which means that the ratio terminal bromide *(2E,4E)*-**4-16**:internal products **4-17+4-18** amounted to only 1.5:1. A second experiment performed in dry CH_2Cl_2 gave a mixture of bromides *(2E,4E)*-**4-16**:*(3E)*-**4-17** 1.7:1 (entry 4). This crude 1.7:1 mixture was purified by flash chromatography. The slightly more polar internal bromide **4-17** underwent partial isomerisation and hydrolysis resulting in a final terminal:internal bromide ratio of 8.7:1 in 67% yield and 18% of internal dienol **4-18**. Compounds **4-16**, **4-17** and **4-18** were characterised on the basis of their NMR spectra. The purified bromides gave better yields in the following alkylation step.

Scheme 4.3 Alkylation experiments



R = Me (6*E*,8*Z*)-**4-20a** R = Me (6*Z*)-**4-21a**
R = Me (6*E*,8*E*)-**4-20a** R = Me (6*E*)-**4-21a**
R = *t*Bu (6*E*,8*E*)-**4-20b** R = *t*Bu (6*E*)-**4-21b**

Table 4.2 Alkylation experiments

Entry	Bromide used **4-16**:**4-17**:**4-18**	Product	**4-20** (%)	**4-21**[a] (%)
1	4.3:1:0 crude	*(6E,8Z)*-**4-20a**	34	6
2	2.3:0.5:1 crude	*(6E,8E)*-**4-20b**	31	not determined
3	3.8:1:0 crude	*(6E,8E)*-**4-20b**	37	not determined
4	8.7:1:0 purified	*(6E,8E)*-**4-20a**	40	3

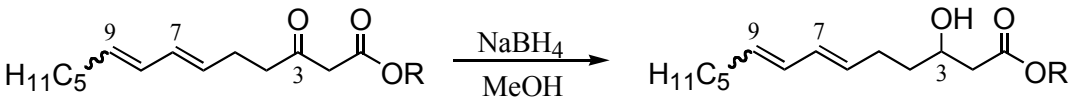
a) Isolated yield based on dienol **4-15**.

The C7-C20 precursors of 15-A_2-IsoP, 3-oxotetradeca-6,8-dienoates *(6E,8Z)*-**4-20a** and *(6E,8E)*-**4-20a,b** were synthesised by alkylation of the dienolate of methyl or *tert*-butyl acetoacetates **4-19a,b** with bromide **4-16** (Scheme 4.3).[127, 129] When the alkylation was performed with the crude mixture of bromides **4-16** and **4-17**, the desired linear 3-oxoesters *(6E,8Z)*-**4-20a** and *(6E,8E)*-**4-20a,b** were obtained in 34%, 31% and 37% isolated yield,

respectively, based on dienol **4-15** (Entries 1, 2, 3). They were accompanied by small amounts of branched regioisomers **4-21**, unreacted acetoacetate **4-19** and further unknown byproducts. Their separation from the product mixtures was often impossible. Keto ester *(6E,8E)*-**4-20a** was synthesised from the purified 8.7:1 mixture of bromides *(2E,4E)*-**4-16** and *(3E)*-**4-17** in 40% overall yield based on dienol *(6E,8E)*-**4-15** accompanied by 3% of *(6E)*-**4-21a** (entry 4). Based on the bromides *(2E,4E)*-**4-16** and *(3E)*-**4-17** the yield of *(6E,8E)*-**4-20a** and *(6E)*-**4-21a** amounted to 66% and 42% yield, respectively.

Keto esters *(6E,8E)*-**4-20a,b** and *(6E,8Z)*-**4-20a** were reduced in good yields with $NaBH_4$ in dry MeOH to cyclisation precursors 3-hydroxytetradeca-6,8-dienoate *(6E,8E)*- and *(6E,8Z)*-**4-11a,b** (Scheme 4.4). Small amounts of the reduced keto ester *(6Z)*-**4-21a** or *(6E)*-**4-21a,b** were rarely isolated.

Scheme 4.4 Preparation of **4-11a,b** from **4-20a,b**



R = Me *(6E,8Z)*-**4-20a** — **4-11a** 83% *(6E,8Z):(6E,8E)* > 8:1
R = Me *(6E,8E)*-**4-20a** — **4-11a** 61% *(6E,8E):(6E,8Z)* > 10:1
R = *t*Bu *(6E,8E)*-**4-20b** — **4-11b** 87% *(6E,8E):(6E,8Z)* = 1:0

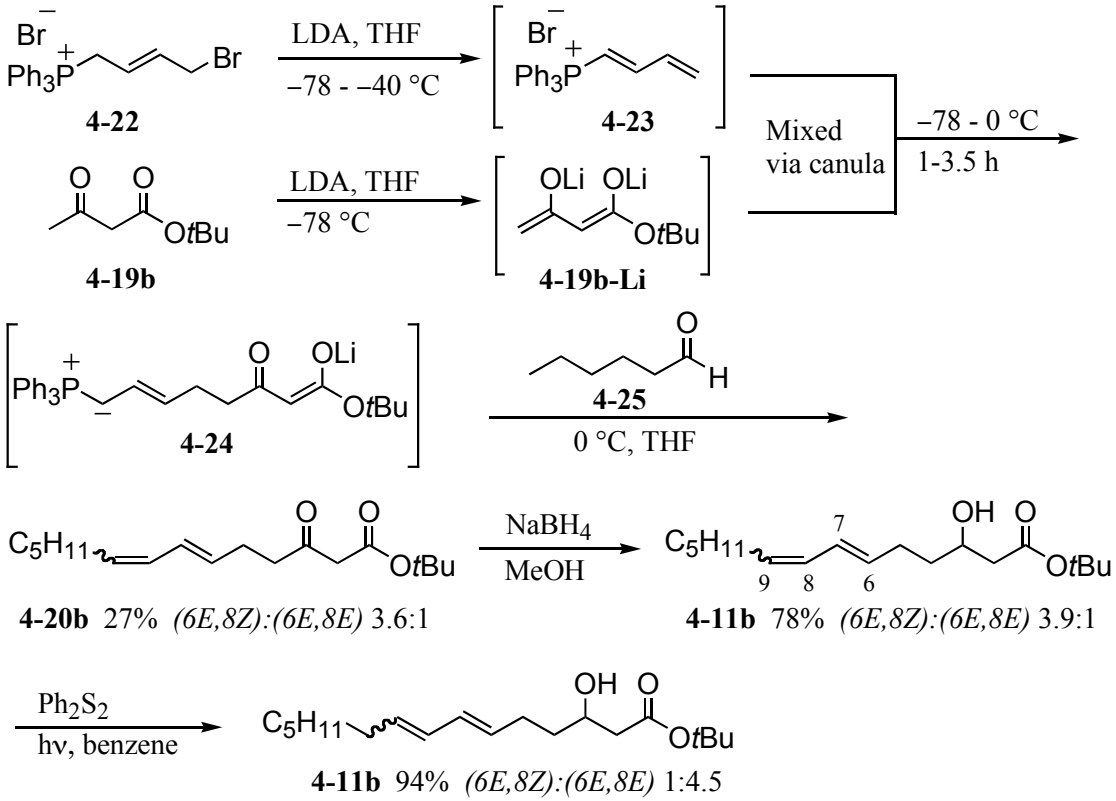
Keto esters *(6E,8E)*-**4-20a,b** and *(6E,8Z)*-**4-20a** displayed a singlet for H2 in the range 3.30-3.45 ppm in the ^{1}H NMR spectra. The double bond resonances exhibited the following trends, depending on their geometry (Table 6.2, Experimental part): For compounds *(6E,8E)*-**4-20a,b**, signals of H8 and H7 as well as H6 and H9 were very close or overlapping. The ^{13}C NMR signals shifted downfield in the order: C6, C8, C7, C9, in the range of 129.0-133.5 ppm. For compounds *(6E,8Z)*-**4-20a**,**b** the signals of the double bond hydrogen atoms were well separated. The ^{1}H and ^{13}C signals shifted upfield in the order: H9, H6, H8, H7 and C7, C8, C9, C6 in the range 5.29-6.33 ppm and 126.7-131.6 ppm respectively. The coupling constants J = 15.0 Hz for H6-H7 in *(6E,8Z)*-**4-20a** and J = 15.1 Hz in *(6E,8Z)*-**4-20b** attested an *(E)*-geometry. Coupling constants of smaller then 11 Hz for H8-H9 in *(6E,8Z)*-**4-20a,b** accounted for a *(Z)*-double bond. The carbonyl group appeared in the range 201.6-202.4 ppm. Hydroxy esters *(6E,8E)*-**4-11a,b** and *(6E,8Z)*-**4-11a,b** showed similar NMR patterns at the double bonds, but C6 and C7 in *(6E,8E)*-**4-11a,b** could not be unambiguously assigned. The ^{1}H NMR signals in the range of 3.96-4.01 ppm and the doublets at 67.2-67.7 ppm were assigned to H3 and C3, respectively.

Key results: Cyclisation precursors 3-hydroxytetradeca-6,8-dienoates *(6E,8E)*-**4-11a,b** and *(6E,8Z)*-**4-11a,b** were synthesised in 30% and 32% yield in 5 and 4 steps respectively. This approach was efficient enough to provide the necessary material for the development of the oxidative cyclisations.

*4.2.1.2. A very short synthesis of (6E,8Z)-**4-11b** and (6E,8E)-**4-11b***

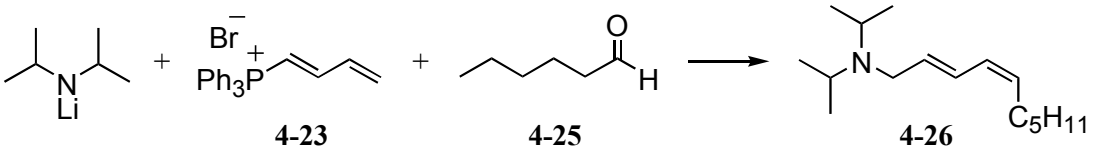
White's three component coupling methodology was adapted to synthesise 3-oxo ester *(6E,8Z)*-**4-20b** (Scheme 4.5).[130] 4-Bromo-2-butenylphosphonium bromide **4-22** was eliminated by LDA to butadienylphosphonium salt **4-23**, which was added to the dienediolate **4-19b-Li**. The resulting allylic phosphonium ylide **4-24** was treated with hexanal **4-25** to provide the oxo ester **4-20b** in 27% yield as a 3.6:1 *(E,Z)/(E,E)* mixture, which was lower than the reported diastereoselectivity.[130] Extensive optimisation attempts varying the amounts of reagents, reaction times and additives did not improve the reaction outcome (Method A, Experimental Part, Table 6.2). Scaling up to gram amounts was, however, accomplished without problems with a yield of 28% (Experimental part, Table 6.2, entry 5).

Scheme 4.5 Synthesis of *(6E,8Z)*-**4-11b** and *(6E,8E)*-**4-11b**



A very polar compound was isolated in significant amounts to which the structure of *N,N'*-diisopropyl-2,4-decadienylamine **4-26** was assigned (Scheme 4.6). The diisopropylamine unit showed a doublet at 3.09 ppm (2H), a septet at 2.97 ppm (2H) and another doublet at 0.93 ppm (12H) in the ^{1}H NMR spectrum. Two double bonds were also identified. The formation of compound **4-26** occurred probably via a competitive nucleophilic addition of LDA or diisopropylamine to butadienyl phosphonium salt **4-23** and a subsequent Wittig reaction with hexanal **4-25**. Sometimes small amounts of the aldol addition product of hexanal and acetoacetate were also detected.

Scheme 4.6 Formation of byproduct **4-26**



4-23 **4-25** **4-26**

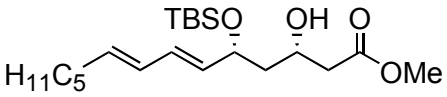
To reduce the amount of diisopropylamine deprotonation of the phosphonium salt **4-22** and acetoacetate **4-19b** was performed in one pot (Method B). The *i*Pr_2NH generated by deprotonation of **4-19b** with LDA was re-deprotonated with BuLi, followed by addition of salt **4-22**. Only 5% of product *(6E,8Z)*-**4-20b** was isolated in a single experiment, besides complex mixtures.

The β-keto ester *(6E,8Z)*-**4-20b** was reduced to β-hydroxy ester *(6E,8Z)*-**4-11b** with $NaBH_4$ in methanol in 78% yield with a d.r. of *(6E,8Z):(6E,8E)* 3.9:1 (Scheme 4.5). The double bond isomer *(6E,8E)*-**4-11b** was synthesised by radical isomerisation of *(6E,8Z)*-**4-11b** in the presence of catalytic amounts of Ph_2S_2 in high yield. β-Hydroxy esters *(6E,8Z)*-**4-11b** and *(6E,8E)*-**4-11b** were synthesised by this approach in two steps with an overall yield of 22% and 21%, respectively, over three steps. However this was not acceptable on larger scale.

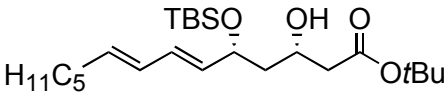
4.2.2. Synthesis of 15-F_{2t}-IsoP 4-1 precursors

The oxidative radical cyclisation methodology developed for *(6E,8Z)*-**4-11a,b** and *(6E,8E)*-**4-11a,b** showed that the (*E,E*)-geometry of the double bonds gives better cyclisation results (*vide infra*). 5-Hydroxy-3-oxoesters **4-28a,b** (cf. Scheme 4.7) cannot serve as substrates, because their cyclisation is known to be too slow.[85] In contrast 3,5-dihydroxy ester derivatives **4-12a** and **4-12b** with (*6E,8E*)-geometry should be good substrates (Figure 4.2).

Figure 4.2 Cyclisation precursors for the synthesis of 15-F_{2t}-IsoP



(6E,8E)-**4-12a**

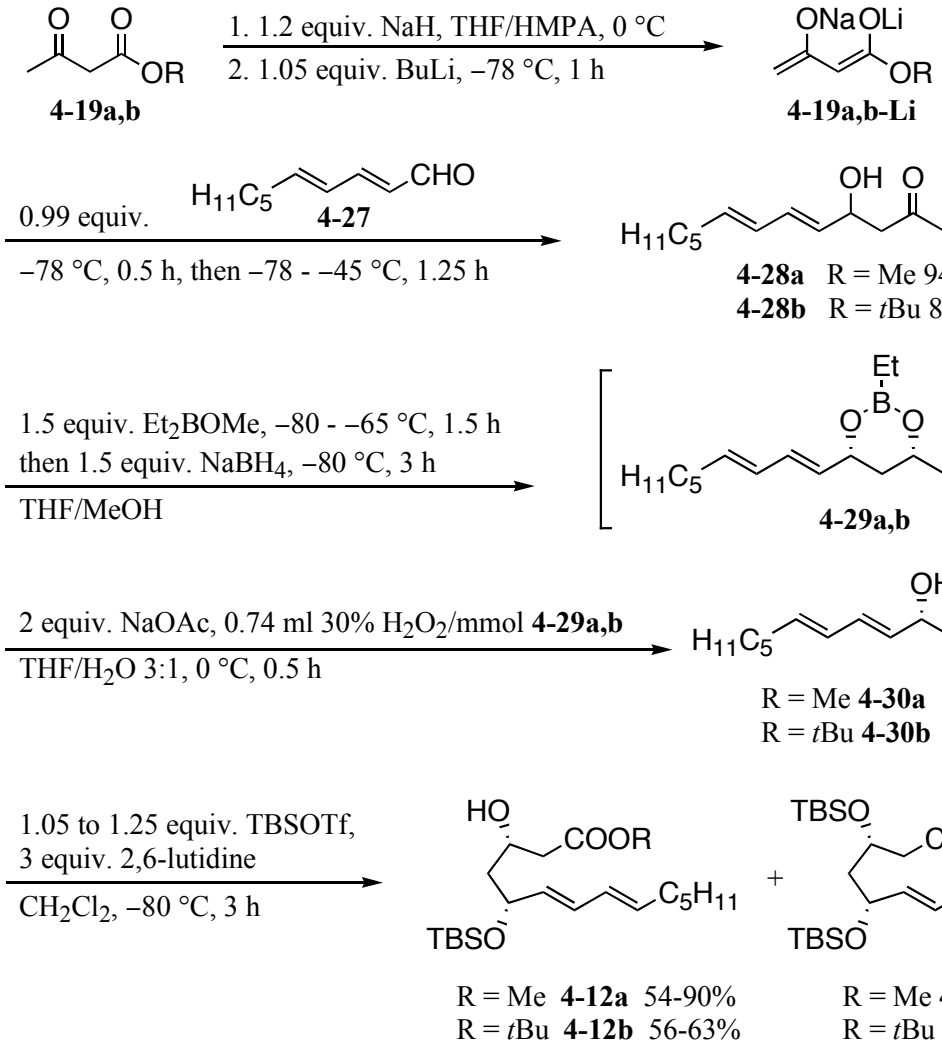


(6E,8E)-**4-12b**

*4.2.2.1. An efficient synthesis of (6E,8E)-**4-12a,b** in 3 steps*

The sequence started with the vinylogous aldol addition[131] of 2,4-decadienal **4-27** and the acetoacetate-derived lithium sodium dienediolate **4-19a**,**b-Li** in THF affording products **4-28a** and **4-28b** in 94% and 81% yields, respectively (Scheme 4.7). HMPA proved to be a necessary additive, since the additions afforded **4-28a** in only 30% yield in its absence. The formation of a colourless solid was often observed during the deprotonation of **4-19a**.

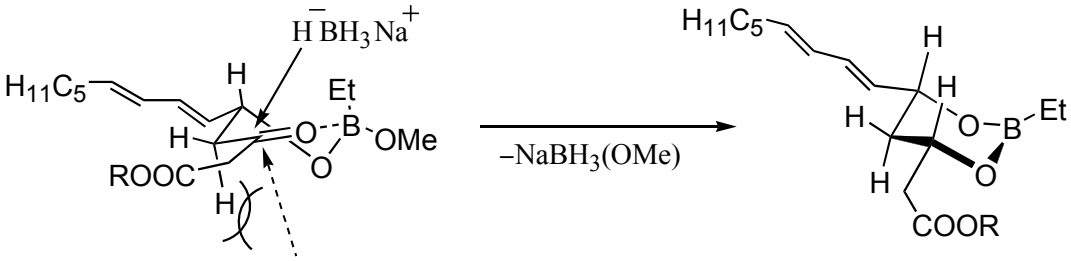
Scheme 4.7 Three-step synthesis of cyclisation precursors **4-12a** and **4-12b**



This indicated that the dienediolate **4-19a,b** formed aggregates, which crystallised from the solution. HMPA, as the best complexation ligand for lithium, breaks the strong

aggregates of the lithium, sodium dienediolates partly and allows the addition to decadienal **4-27**. The immediate reduction of the somewhat labile β-keto esters **4-28a,b** with $NaBH_4$, in the presence of Et_2BOMe furnished *syn*-diols **4-30a,b** in good yields via the boronates **4-29a,b**.[132] The reaction proceeds via initial formation of a boronate chelate **4-A** with release of ethane (Scheme 4.8). This intermediate controls the attack of the hydride ion from the more accessible β-face via transition state **4-A**, thus avoiding the interaction with the axial hydrogen atom on the α-face. This leads to the formation of *syn*-boronates **4-29a,b**. Boronates **4-29a,b** were successfully deprotected with hydrogen peroxide in the presence of NaOAc.[133] Other boronate-hydrolysing methods proved not to be powerful enough for this substrate.

Scheme 4.8 Formation of boronate **4-29a,b**



4-A **4-29a,b**

(6E,8E)-3,5-Dihydroxy-6,8-tetradecadienoate **4-30a** underwent a regioselective silylation with TBSOTf in the presence of 3 equivalents of 2,6-lutidine in CH_2Cl_2 at –78 °C (Table 4.3).[134] This reaction proved to be unique, since other protective groups did not lead to any selectivity.[135]

Table 4.3 Silylation condition for **4-30a** and **4-30b**

Entry	Substrate	Equiv. TBSOTf	Setup and conditions	**4-12** (%)	**4-31** (%)
1	**4-30a**	2	0.8 mmol, –78 °C	71	29
2	**4-30a**	1.5	0.8 mmol, 1.2 equiv TBSOTf, –78 °C, 4 h, then 0.3 equiv. TBSOTf, –78 °C, 10 min	90	10
3	**4-30a**	1.25	1.33 mmol, –78 °C	82	6
4	**4-30a**	1.05	8.3 mmol, –78 °C, 1.5 h; –78 - –60 °C, 2 h	79[a]	trace
5	**4-30a**	1.05	8 mmol, –78 °C, 1.5 h; –78 - –40 °C, 2.5 h	54	18
6	**4-30b**	1.2	3.4 mmol, –78 °C, 2.5 h	65	22
7	**4-30b**	1.05	9.5 mmol, 1 h –78 °C	63	7
8	**4-30b**	1.05	10.7 mmol, 2.5 h –78 °C	56	23

[a] 19% substrate was recovered.

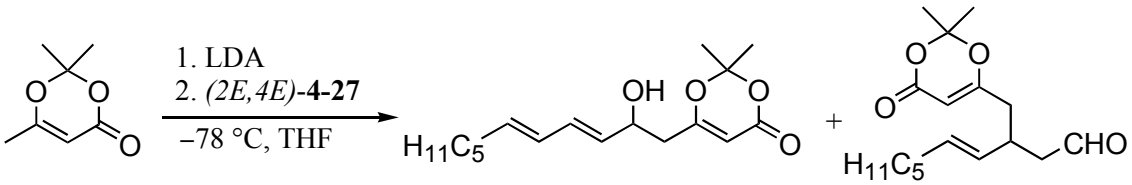
Methyl *(6E,8E)*-5-silyloxy-3-hydroxy-6,8-tetradecadienoate **4-12a** was obtained in 54-90% yield, while the disilylated *(6E,8E)*-3,5-bis(silyloxy)-6,8-dienoate **4-31a** formed only in yields of 6-29%. The amount of TBSOTf as well as the temperature influenced the silylation yield and selectivity. An experiment performed with 2 equivalents of TBSOTf at −80 °C led to 71% of monosilylated product **4-12a** and 29% yield of disilylated product **4-31a** (entry 1). The silylation with 1.5 equiv. of TBSOTf added in two portions was the most successful (entry 2). Product **4-12a** was obtained in 90% yield and the byproduct **4-31a** in 10% yield. High yields were also obtained with 1.25 and 1.05 equiv. of TBSOTf (entries 3 and 4), where the formation of disilylated **4-31a** was minimal. It proved to be important, however, to keep the temperature low all time to avoid increased formation of **4-31a** (entry 5). The selectivity was generally lower for **4-30b** (entries 6-8). Monosilylated **4-12b** was isolated in 56-65% yields, while the byproduct **4-31b** formed in 7-23% yield. The reaction at the α-dienyl hydroxy group was kinetically favoured due to electronic effects induced by the diene unit.

The cyclisation substrates **4-12a** and **4-12b** were thus efficiently synthesised in 3 steps from 2,4-*(E,E)*-decadienal **4-27** in overall yields of 72% and 41%, respectively.

*4.2.2.2. A synthesis of (6E,8E)-**4-12b** in 4 steps*

The synthesis of the 15-F_{2t}-IsoP starting materials was alternatively approached by a vinylogous aldol addition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **4-32** with *(2E,4E)*-deca-2,4-dienal **4-27** (Scheme 4.9).[136]

Scheme 4.9 Aldol addition of dioxinone **4-32** and decadienal **4-27**



4-32 **4-33** 43% **4-34** 30%

Table 4.4 Optimisation of the aldol reaction of **4-32** to **4-27** on a 2 mmol scale

Entry	Reaction time	T (°C)	Solvent	**4-33** (%)	**4-29** (%)
1	45 min	−78	THF	43	30
2	45 min	−78	THF/HMPA	53	-
3	25 min	−78	THF	56	31
4	**15 min**	**−90**	**THF**	**63**	**-**
5	120 min	−78 - −30	THF	53	-

The aldol adduct **4-33** was obtained under basic conditions at −78 °C in a moderate 43% yield (Table 4.4, entry 1). It was accompanied by a Michael addition product **4-34** resulting from the attack of the lithium enolate of dioxinone **4-32** to the 3-position of the decadienal **4-27** which was isolated in 30% yield. Addition of HMPA suppressed the formation of **4-34**, but the yield of **4-33** was only slightly improved (entry 2).

Since the aldol reaction is reversible and kinetically favoured over the Michael addition, which is slow and forms the thermodynamically more stable product,[107c-f] the reaction was optimised with respect to reaction time and temperature (entries 3-5). The best yield of **4-33** (63%) was obtained at the shortest reaction time of 15 min and the lowest temperature of −90 °C (entry 4). Michael adduct **4-34** was not formed under these conditions. However **4-34** was not always isolated despite longer reaction time and higher temperatures, but the mass balance was low (entry 5).

Table 4.5 Significant NMR chemical shifts and multiplicities of compounds **4-33** and **4-34**.

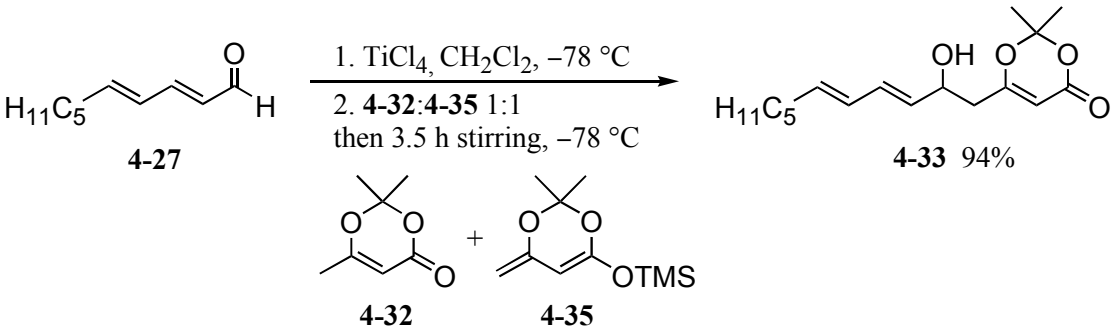
	*CH*OH *or CH*O	*CH*COO	CH_2C(O)=CH	*CH*=*CH*CH or CH_2CHO	*CH*=*CH*CH_2
4-33	4.39 (dt)	5.28 (s)	2.42, AB part of	6.19 (dd), 5.52 (dd)	5.97 (dd), 5.70 (dt)
	69.6 (d)	95.2 (t)	ABX, 41.5 (t)	132.3 (d), 130.9 (d)	128.8 (d), 137.0 (d)
4-34	9.64 (t)	5.15 (s)	2.29, 2.17, AB part	2.42 (dd)	5.45 (dt), 5.18 (ddt)
	200.8 (d)	94.7 (d)	of ABX, 39.0 (t)	48.3 (t)	133.2 (d), 129.9 (d)

The structure of **4-33** was assigned by means of its NMR data (Table 4.5). The diene resonances were found in the range 5.52-6.19 ppm (^{1}H NMR) and 128.8-137.0 ppm (^{13}C NMR), respectively. A singlet at 5.28 ppm (^{1}H NMR) corresponding to a doublet at 95.2 ppm (^{13}C NMR), and a singlet at 168.5 ppm (^{13}C NMR) accounted for the double bond of the dioxinone unit, whose presence was proved also by the signal of the lactone unit =CH*C*O_2 at 161.2 ppm (s) and the quaternary carbon of the acetal at 106.7 ppm (s). The allylic CH bearing the hydroxy group appeared as a doublet of triplets at 4.39 ppm (^{1}H NMR) and a doublet at 69.6 ppm (^{13}C NMR), respectively. The Michael addition product **4-34** was characterised by the presence of the dioxinone unit and the resonances of only one double bond. In addition, a triplet at 9.64 ppm (^{1}H NMR) corresponding to a doublet at 200.8 ppm (^{13}C NMR) proved the presence of the aldehyde.

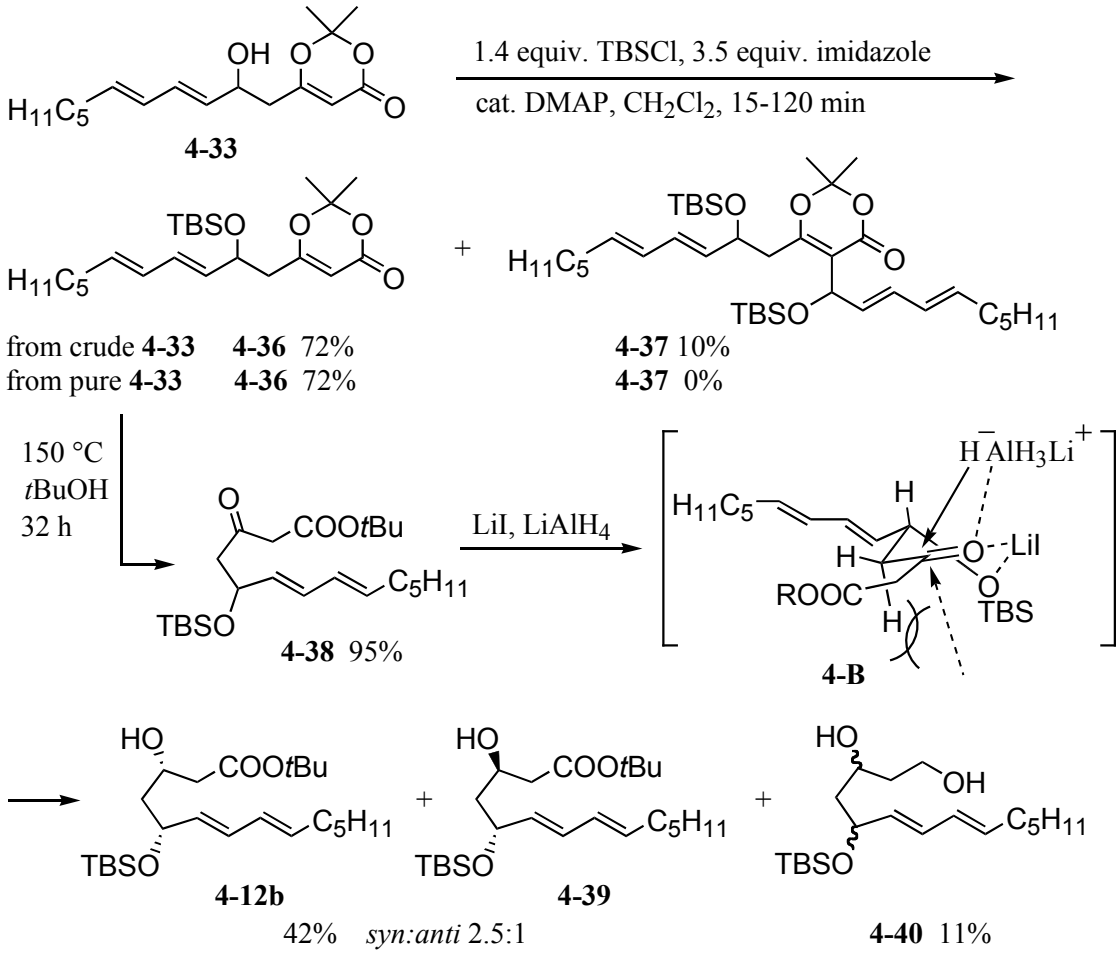
The Mukaiyama aldol addition of the trimethylsilyl ketene acetal **4-35** and decadienal **4-27** in CH_2Cl_2 in the presence of $TiCl_4$ was chosen as an alternative approach to **4-33**

(Scheme 4.10).[137] The trimethylsilyl ketene acetal **4-35** was synthesised according to a literature procedure, but was obtained as an inseparable mixture with **4-32**.[138] The reaction with **4-27** was performed by adding excess of this mixture until **4-27** was consumed. Hydroxydioxinone **4-33** was obtained in 94% yield based on **4-27**.

Scheme 4.10 Mukaiyama aldol addition for the synthesis of **4-33**



Scheme 4.11 Synthesis of cyclisation precursor **4-12b**



The protection of pure **4-33** with TBSCl in the presence of imidazole and a catalytic amount of DMAP afforded product **4-36** in 72% yield (Scheme 4.11). A similar protection of

crude **4-33**, which contained small amounts of **4-27**, gave product **4-36** in 72% yield. Moreover, a Baylis-Hillman-type reaction occurred competitively under the reaction conditions giving 10% of **4-37**, which was, however, easily separated by flash chromatography.

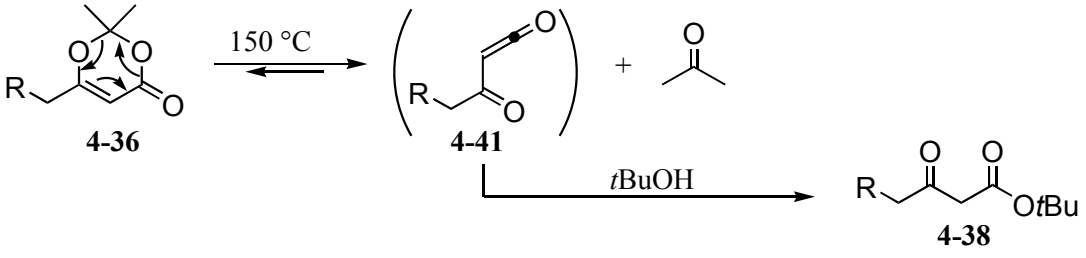
The structures of **4-36** and **4-37** were unambiguously assigned by means of their NMR data (Table 4.6). Characteristic signals of the dioxinone unit and of the diene unit were identified. The doublet of triplets at 4.31 ppm (^{1}H NMR), corresponding to its doublet in ^{13}C NMR at 70.5 ppm was assigned to the CH unit bearing the silyl ether group. The neighbouring methylene group corresponds to the AB part of an ABM system. The byproduct **4-37** exhibited clearly signals of two diene groups, two silyl ether groups and a dioxinone unit. The fifth double bond belonging to the dioxinone showed two quaternary carbon atoms in the ^{13}C NMR spectrum, which indicated substitution at the C5-position.

Table 4.6 Significant NMR chemical shifts and multiplicities of **4-36** and **4-37**.

Product	*CH*OTBS	*CH*$_2$CHOTBS	*CH*COO or *C*COO	*CH*=*CH*CH$_2$	*CH*=*CH*CHOTBS
4-36	4.31 (dt) 70.5 (d)	2.30 (AB part of ABM), 43.1 (t)	5.16 (s) 95.3 (d)	5.88 (dd), 5.59 (dt) 136.6 (s), 129.0 (s)	6.02 (dd), 5.39 (dd) 131.9 (d), 131.1 (d)
4-37	5.34 (d), 4.37 (m) 67.5 (d), 70.5 (d)	3.01, 2.32 (AB part of ABM), 40.3 (t)	- 109.6 (s)	5.90 (dd), 5.57 (m) 135.5 (d), 134.7 (d) 129.6 (d), 129.3 (d)	6.06 (dd), 5.40 (dd) 133.1 (d), 132.4 (d) 130.8 (d), 129.5 (d)

tert-Butyl β-keto ester **4-38** was obtained by transesterification of **4-36** with *t*BuOH at high temperature (Scheme 4.11).[139] The reaction proceeds probably by a retro-Diels-Alder reaction forming the acyl ketene **4-41**, followed by the addition of *tert*-butanol (Scheme 4.12).

Scheme 4.12 Conversion of dioxinone in a 3-oxo-ester



An attempted reduction of β-keto ester **4-38** with $LiAlH_4$/LiI proceeded in low yield and with a moderate 2.5:1 *syn:anti* selectivity (Scheme 4.11).[140] The attack of $LiAlH_4$ occurred preferentially at the least hindered face of a six-membered cyclic transition state like **4-B** leading to the formation of an excess of *syn*-**12b**. Moreover, the triol **4-40** was also formed by reduction of the ester function. The *syn*-**4-12b** and *anti*-**4-39** isomers were not separable by flash chromatography. The reduction of **4-38** with $NaBH_4$ did not occur with any selectivity. Since oxidative radical cyclisations with mixtures of *syn*-**4-12b** and *anti*-**4-39** as precursors would have doubled the number of products (*vide infra*), this approach via **4-38** was given up. To improve the reduction one could deprotect **4-38** to **4-28b**, but that would result in a larger number of steps.[141]

The structures of products **4-38**, **4-12b** and **4-39** were assigned based on their NMR data (Table 4.7). The connectivity was approved by COSY and HSQC measurements. For keto ester **4-38** the methylene group adjacent to the ester group displays a singlet at 3.34 ppm (^{1}H NMR) and a triplet at 52.1 ppm (^{13}C NMR). The ketone appeared as a singlet at 201.5 ppm. A doublet of triplets at 4.60 ppm and a ^{13}C NMR resonance at 70.1 ppm was assigned to the CH group bearing the TBS-oxy group. Alcohols *syn*-**4-12b** and *anti*-**4-39** had only slightly different spectra.

Table 4.7 Significant NMR chemical shifts and multiplicities of δ-silyloxy-β-keto ester **4-38**, *syn*-**4-12b** and *anti*-**4-39**

Product	*CH*OTBS	*CH*$_2$CHOTBS	CH$_2$*C*OCH$_2$ or *CH*OH	*CH*$_2$COO*t*Bu
4-38	4.60 (dt), 70.1 (d)	2.75, 2.55 (AB part of ABX), 51.2 (t)	-, 201.5 (s)	3.34 (s), 52.1 (t)
4-12b	4.30 (dt), 72.8 (d)	1.67 (ddd), 1.51 (ddd), 44.5 (t)	4.01 (m), 66.6 (d)	2.30 (AB part of ABM), 42.7 (t)
4-39	4.45 (m), 71.1 (d)	1.62 (m), 1.54 (m), 43.9 (t)	4.17 (m), 65.2 (d)	2.33 (m), 43.1 (t)

4.2.3. Attempts toward an asymmetric synthesis of 15-F$_{2t}$-IsoP precursors

The isoprostanes are biosynthesised as racemates. Nonetheless it is interesting to attempt their synthesis enantioselectively, since the individual enantiomers may display significant differential biological activity. This requires to secure their absolute configuration early in the synthesis, best already in the initial aldol addition, from which all other stereocentres can be introduced subsequently in a controlled manner as shown before.

4.2.3.1. Studies on enantioselective aldol additions to control the stereocentre in 11-position

Literature precedent on asymmetric vinylogous aldol additions[142] indicated that enantioselective Mukaiyama-aldol additions of the silyl ketene acetal **4-35** and decadienal **4-27** are promising (Scheme 4.13, Table 4.8). The aldol addition was performed using a Ti(IV)/*(R)*-BINOL complex as the catalyst under conditions similar to those employed by De Rosa et al.[143] The chemical yield was good in all cases, the enantiomeric excess remained however moderate at best. The best enantiomeric excess of 71% was obtained by using powdered molecular sieves (entry 3 vs. 1,2). The *ee* of product **4-33** was determined by HPLC with a DAICEL-OD chiral column.

Scheme 4.13 Enantioselective Aldol Addition applying De Rosa's method

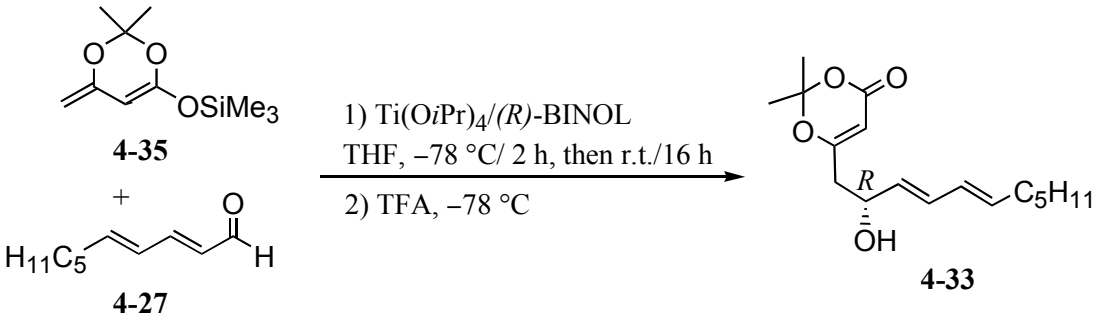
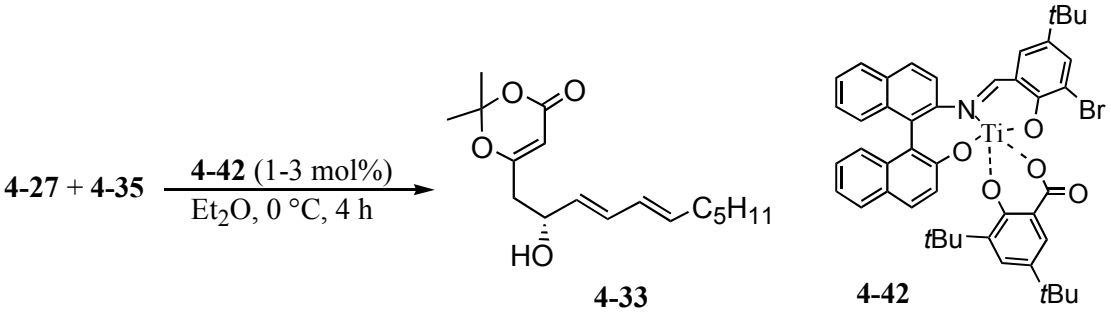


Table 4.8 Optimisation of enantioselective aldol addition

Entry	**4-35**:**4-27**:Catalyst	Molecular sieves 4Å (g/mmol cat.)	Time (min) cat. + **4-27**	Yield (%)	%*ee*
1	0.94 : 0.47 : 0.08	spheric; 0.6/0.08	45	68	40
2	2 : 1 : 0.08	spheric; 0.6/0.08	40	74	19
3	2 : 1 : 0.08	powder; 0.35/0.08	20	72	71

Since 71% *ee* was not good enough to continue the synthesis on larger scale, the aldol reaction was also performed using Carreira's catalyst **4-42**.[138, 139, 144] The catalyst was generated *in situ*. The substrates **4-27** and **4-35** were stirred in the presence of 1-3 mol% of **4-42** at 0 °C for 4 h. The product **4-33** was isolated in a good 73% yield, but the enantiomeric excess amounted to only 11%. To optimise this reaction, more detailed investigations on this as well as on other catalysts or chiral Lewis acids[142a] are necessary.

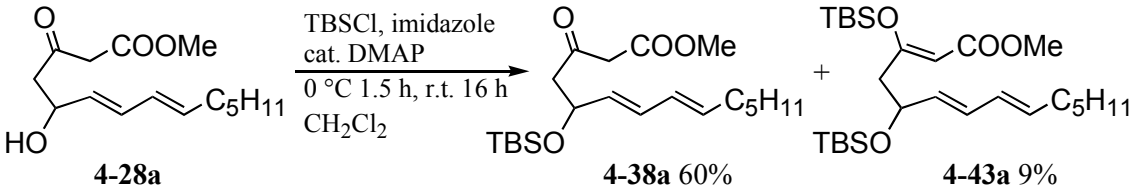
Scheme 4.14 Carreira's asymmetric Mukaiyama aldol additions



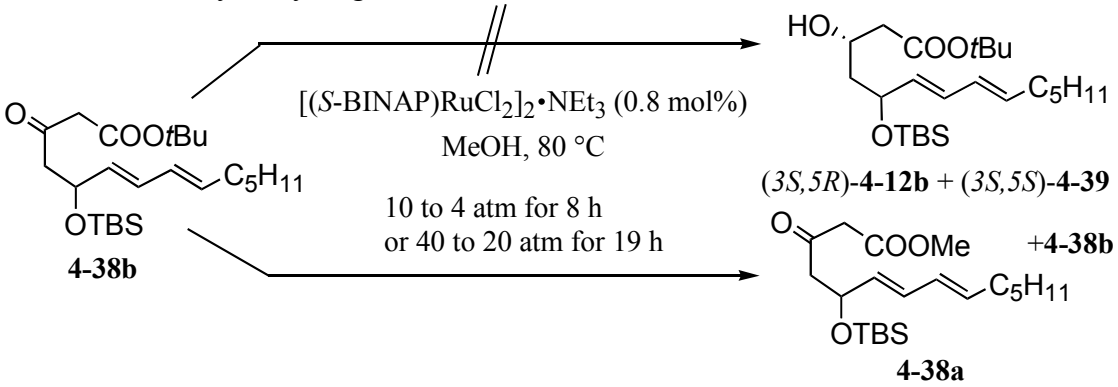
4.2.3.2. Studies on asymmetric hydrogenations to control the stereocentre in 9-position

The 5-silyloxy-3-keto ester **4-38a** precursor was synthesised by a standard silylation of **4-28a** in 60% yield (Scheme 4.15). Noyori's catalyst was generated according to literature procedures.[145] Hydrogenation of the methyl ester **4-38a** afforded complex mixtures. Catalytic hydrogenations of 5-silyloxy-3-oxo ester **4-38b** were investigated under conditions described in Scheme 4.16. No hydrogenation was observed. The starting material accompanied by some undefined compounds was recovered and small amounts of the methyl ester **4-38a** were sometimes isolated as a result of a transesterification reaction. The investigations were not continued.

Scheme 4.15 Silylation of **4-28a**



Scheme 4.16 Noyori hydrogenation of **4-38b**



Alternatives might consist in biocatalytic reduction of **4-38** with baker's yeast, which would give the product with (*S*)-configuration.[146]

4.3. Development of oxidative radical cyclisations for the synthesis of 2-hydroxy cyclopentane carboxylates

To develop an efficient approach to the synthesis of cyclopentanes **4-7a,b** and **4-8a,b** with isoprostane configuration (cf. Scheme 4.1) the diastereoselectivity of the cyclisation has to be controlled. The investigations were concentrated on the following aspects:

A. The influence of structural factors of cyclisation substrates like double bond geometry, the substituent in the 11-position and the ester group on the yields and diastereoselectivity of the oxidative radical cyclisations.

B. The coordination strength of the metal counterion and the properties of the enolate intermediate should play an important role in the control of diastereoselectivity by influencing the transition state of the radical cyclisation.

4.3.1. Development of cyclisations with A_2-isoprostane precursors (6E,8Z)-4-11a,b and (6E,8E)-4-11b

Esters **4-11a,b** were subjected to dideprotonation with excess LDA followed by treatment with TEMPO **1-2** and ferrocenium hexafluorophosphate **1-3** (Scheme 4.17). HMPA was known to improve conversion of similar radical cyclisations,[25] therefore it was employed constantly as an additive. Cyclopentane carboxylates with isoprostane configuration **4-7a,b** and prostaglandin configuration **4-45a,b** were isolated as the main products of the radical cyclisation of 3-hydroxy esters *(6E,8Z)*- and *(6E,8E)*-**4-11a,b**. Four other cyclopentane isomers **4-46a,b** were isolated in small amounts, however, their ring configuration could not be established. The TEMPO trapping occurred highly regioselectively in the 15-position. Small quantities of acyclic **4-48a,b** were also isolated and small amounts of substrate were recovered.

Substrates **4-11a,b** with *(6E,8Z)*-configuration were converted into **4-7a,b** and **4-45a,b** in moderate yields of 51-60% in a roughly 1:1 ratio (Table 4.9, entries 1-3). The size of the ester functionality did not influence the outcome.

Scheme 4.17 Oxidative radical cyclisations of **4-11a,b**

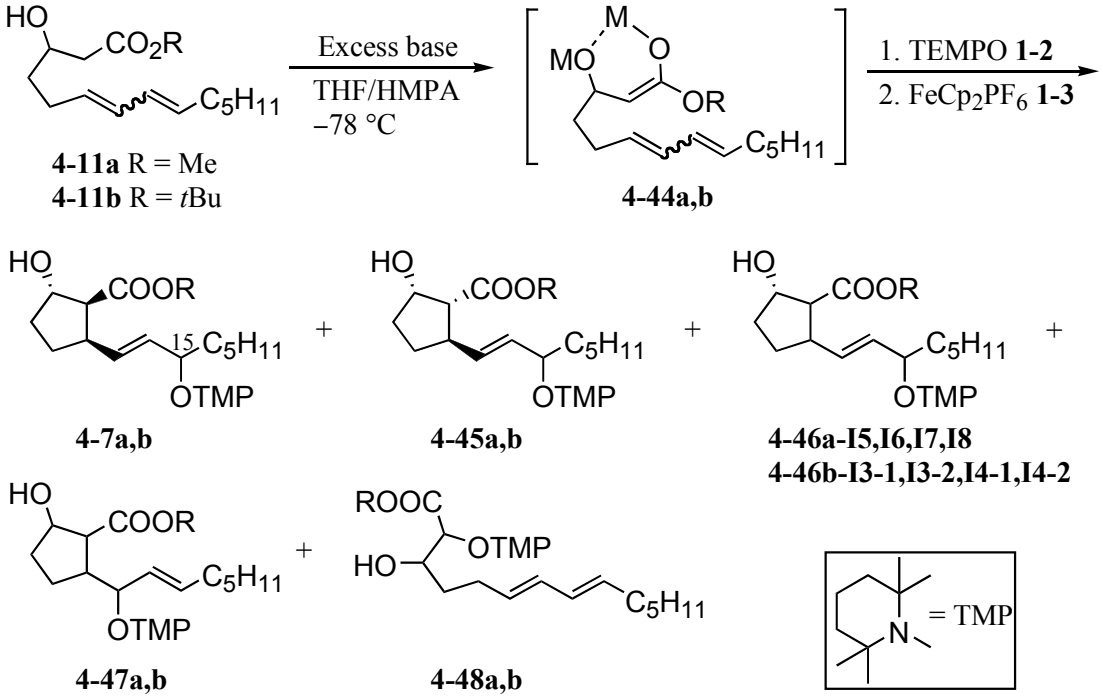


Table 4.9 Cyclisation experiments – Investigation on the influence of the ester group R and the double bond geometry

Entry	Substrate	Equiv. base/ equiv. additives	**4-7**+**4-45**+**4-46** (%)	**4-7**(α/β)[a]**:4-45**(α/β)**: 4-46**	**4-48** (%)
1[b]	*(E,Z)*-**4-11b**	2.5 LDA/ 2.6 HMPA	51	6.5(1:5.4):5.2(1:1.1):1	-
2[c]	*(E,Z)*-**4-11a**	2.5 LDA/ 2.5 HMPA	60	1.7(1:3):2.2(1:1):1	5
3[d]	*(E,Z)*-**4-11a**	2.5 LDA/ 6 HMPA	58	3.6(1:2.5):3.7(1.2:1):1	2
4[e]	*(E,E)*-**4-11b**	2.5 LDA/ 2.5 HMPA, 7 LiCl	66	2.7(2.4:1):1.8(1:2.3):1	2
5[f]	*(E,E)*-**4-11a**	2.5 LDA/ 6 HMPA	75	2.6(3.1:1):1.8(1:2.3):1	10
6[g]	*(E,E)*-**4-11a**	2.5 LDA/ 6 HMPA, 12 LiCl	70	2.9(3.8:1):1.45(1:2.3):1	19

a) α/β refers to the orientation of the tetramethylpiperidinyloxy group in the 15-position. b) Setup 2.34 mmol, 31% of **4-11** recovered, **4-46b-I3-1**,**2**. c) Setup 0.79 mmol, 4% of **4-11** recovered, **4-46a-I5**, **I7**, and **I8**. d) Setup 0.79 mmol, **4-46a-I7** and **I8**. e) Scale up 3.37 mmol, 10% of **4-11** recovered, **4-46b-I3-1,2** and **I4-1,2**; **4-47** 6%. f) Setup 1 mmol, 3% of **4-11** recovered, **4-46a-I5**, **I6** and **I7**. g) Setup 1 mmol, 10% of **4-11** recovered, **4-46a-I6**, **I7** and **I8**.

Cyclisations of *(6E,8E)*-**4-11a,b** afforded cyclopentanes **4-7a,b**, **4-45a,b** and **4-46a,b** in improved yields of 66, 75 and 70%, respectively (Table 4.9, entries 4, 5 and 6). The main products **4-7a,b** and **4-45a,b** were formed with slightly improved diastereoselectivity. The desired isoprostane-configurated products **4-7a,b** were the major diastereomers. The ring diastereomers **4-46a,b** were isolated in small amounts. Small quantities of regioisomeric trapping products **4-47b** were detected on scale-up of the reaction (entry 4). The highest conversion was realised with methyl ester *(6E,8E)*-**4-11a** in the presence of 6 equivalents of HMPA, which gave the cyclisation products in 75% yield (entry 5). Acyclic **4-48a** was formed in 10% yield. In the presence of 12 equivalents of LiCl, a 2:1 diastereoselectivity of **4-7a**:**4-45a** was achieved, although the cyclisation was apparently slightly slowed down, since acyclic **4-48a** was isolated in increased 19% yield (entry 6). The 15α/15β-diastereoselectivity was variable. Two trends were observed depending on the 6,8-double bond geometry. The isomer 15β-**4-7a,b** was preferentially obtained from *(6E,8Z)*-**4-11a,b**, while *(6E,8E)*-**4-11a,b** furnished mainly 15α-**4-7a,b**. No selectivity was found for 15α- and 15β-**4-45a,b** when *(6E,8Z)*-**4-11a,b** was the precursor, while *(6E,8E)*-**4-11a,b** provided 15β-**4-45a,b** as the major diastereomer. The formation of both, the 15α- and 15β-isomers, does not matter at this stage, since this stereocentre will be destroyed later by oxidative deprotection of the 2,2,6,6-tetramethylpiperidinyl unit.

Table 4.10 Cyclisations experiments – investigation of different metal ions

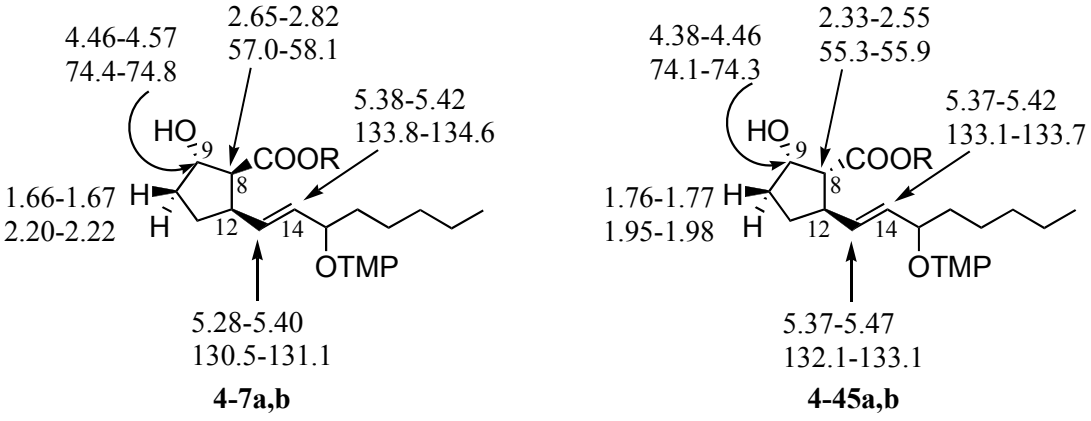
Entry	Substrate	Equiv. base/ additives	**4-7+4-45 +4-46** (%)	**4-7**(α/β)**:4-45**(α/β)**:4-46**	**4-48** (%)
1[a]	*(E,Z)*-**4-11b**	4 LDA/2.6 HMPA	53	4.8(1:6.9):4.8(2.3:1):1	-
2[b]	*(E,Z)*-**4-11b**	1.5 MeMgCl, 1.3 LDA/2.7 HMPA	28	1(1:0):10.5(1:2.1):2.5	22
3[c]	*(E,Z)*-**4-11a**	1.2 *t*BuMgCl, 1.3 LDA/6.3 HMPA	49	1(1:2):8.5(1.7:1):2.7	15
4[d]	*(E,E)*-**4-11a**	1.5 *t*BuMgCl, 1.5 LDA/6.3 HMPA	45	1(2.5:1):5.8(1:1.3):0.7	4
5[e]	*(E,E)*-**4-11b**	1.2 *t*BuMgCl, 1.3 LDA/6.3 HMPA	52	1(3.3:1):5.8(1:2.2):1.8	10
6[f]	*(E,E)*-**4-11b**	1.5 *t*BuMgCl, 2.2 LDA/6.3 HMPA	49	1:19.5(1:1.9):4	4

a) Setup 0.34 mmol, **4-11** 13%, **4-46b-I3-1,2** and **I4-1,2**. b) Setup 0.57 mmol, **4-11** 19%, **4-46b-I4-1,2**, **4-47** 3%. c) Setup 0.79 mmol, **4-11** 17%, **4-46-I5** and **I6**. d) Setup 0.79 mmol, **4-11** 7%, **4-46-I5** and **I6**. e) Setup 1 mmol, **4-11** 24%, **4-46b-I4-1,2**, **4-47** 6%. f) Setup 1 mmol, **4-11** 9%, **4-46b-I3-1,2** and **I4-1,2**, **4-47** 9%.

The cyclisation outcome depended significantly on the applied deprotonation conditions. An excess of LDA (4 equivalents) in deprotonation of *(6E,8Z)*-**4-11b** led to a decrease in diastereoselectivity **4-7a,b**/**4-45a,b** to 1:1 (Table 4.10, entry 1 versus Table 4.9, entry 1). Sequential deprotonation of **4-11a,b** with a slight excess of Grignard reagent and then LDA switched the **4-7a,b**:**4-45a,b** diastereoselectivity to 1:5.8-19.5, hence **4-45a,b** was by far the major diastereomer (Table 4.10, entries 2-6). Cyclopentanes **4-46** were formed in similar yields as before. However, the overall conversion was lower and larger amounts of substrate **4-11** were recovered. Acyclic **4-48** also formed to a relatively large extent (entries 2, 3 and 5). When deprotonation of **4-11b** was conducted with Et_2Zn followed by LDA, no cyclisation occurred and the substrate was recovered.

The structure of **4-7a,b** and **4-45a,b**-**4-48a,b** was established by ^{1}H and ^{13}C NMR spectroscopy, especially by COSY and HSQC experiments. The chemical shifts of positions 8, 9, 10, 12, 13 and 14 were significant for the assignment of the ring diastereomers (Figure 4.3, Experimental part, Table 6.4). The proton at C8 of IsoP isomers **4-7a,b** was downfield-shifted by 0.24-0.33 ppm compared to the PG isomers **4-45a,b**. Similarly C8 of **4-7a,b** was downfield shifted by 1.7-2.5 ppm compared to C8 of **4-45a,b**. The same trend, but less pronounced, was ascertained for the 9-position. Chemical shifts of H10 were also relevant for the assignment of ring diastereomers. While the differences between H10α and H10β of IsoP **4-7a,b** amounted 0.54-0.55 ppm, these protons absorbed much closer to each other in PG isomers **4-45a,b**, with a difference of only 0.22 ppm. The chemical shift difference of the vinyl carbon atoms C13 and C14 were also crucial to distinguish between the ring diastereomers. IsoP isomers **4-7a,b** exhibited larger differences Δ(δC14-δC13) of 2.9-3.7 ppm than PG isomers **4-45a,b**, which displayed differences of only 0.3-1.0 ppm.

Figure 4.3 Significant NMR data of compounds **4-7a,b** and **4-45a,b**



The relative ring configuration of 15β-**4-45a** and 15β-**4-7b** was confirmed by NOE measurements. Common patterns of the NMR data for diastereomers with the same ring configuration but different relative configuration in 15-position were ascertained. The α- and β-diastereomers in 15-position were assigned by comparison of the ^{13}C NMR data with those of model compounds.[85]

Key results:

- A new cyclisation method for the synthesis of A_2-isoprostane and PG A_2 ring systems **4-7a,b** and **4-45a,b** was developed. The best yields of cyclic products amounted to 70-75%.
- The double bond geometry of substrates **4-11a,b** had an influence on the diastereoselectivity of the radical cyclisation of the dilithium dianion **4-44a,b**. *(6E,8Z)*-**4-11a,b** cyclised less selectively than *(6E,8E)*-**4-11a,b**, which gave **4-7a,b** with isoprostane configuration in excess.
- Modification of the deprotonation conditions to RMgCl/LDA led to a switch of diastereoselectivity **4-7a,b**:**4-45a,b** from 2:1 to 1:6-19 in favour of cyclopentanes with prostaglandin configuration. The yield of the reactions were however, lower.
- The reaction was scaled up to gram amounts without problems. The *tert*-butyl esters **4-7b** and **4-45b** were more easily separable than the methyl esters **4-7a** and **4-45b**.

4.3.2. Cyclisations with F_{2t}-isoprostane substrates 4-12a,b

The cyclisation conditions developed for the synthesis of the A_2-isoprostane skeleton **4-7a,b** were adapted to assemble the F_{2t}-IsoP ring system **4-8a,b** with substrates *(6E,8E)*-**4-12a** and *(6E,8E)*-**4-12b** (Scheme 4.18). The oxidative cyclisations of the dilithium alkoxido-enolate **4-49a,b** generated by deprotonation of **4-12a** and **4-12b** with LDA furnished cyclopentanes **4-8a,b** and **4-50a,b** in yields of 71% and 58%, respectively, accompanied by minute amounts of another isomer **4-51a,b** (Table 4.11, entries 1-2). From the methyl ester **4-12a**, the 15α/β-isoprostane isomers **4-8a** were formed in a slight excess over **4-50a**. The cyclic proximal products **4-52a,b** were also detected in noticeable yields of 1-8%.

The generation of lithium-magnesium alkoxido-enolates **4-49a,b** induced a switch of diastereoselectivity in favour of products **4-50a,b** with prostaglandin configuration. The yields were moderate, but the PG:IsoP ratio (**4-50**:**4-8**) amounted to 4-6:1 (entries 3-4). The stronger chelation by Mg^{2+} decreased the cyclisation rate, hence higher amounts of **4-12a,b** were recovered and the acyclic TEMPO trapping product **4-53** was isolated in 17-19% yield.

These results confirmed that the cyclisation conditions developed for substrates **4-11a,b** were generally applicable to more complex substrates **4-12a,b** containing the additional stereocentre in 5-position.

Scheme 4.18 Oxidative radical cyclisations of **4-12a,b**

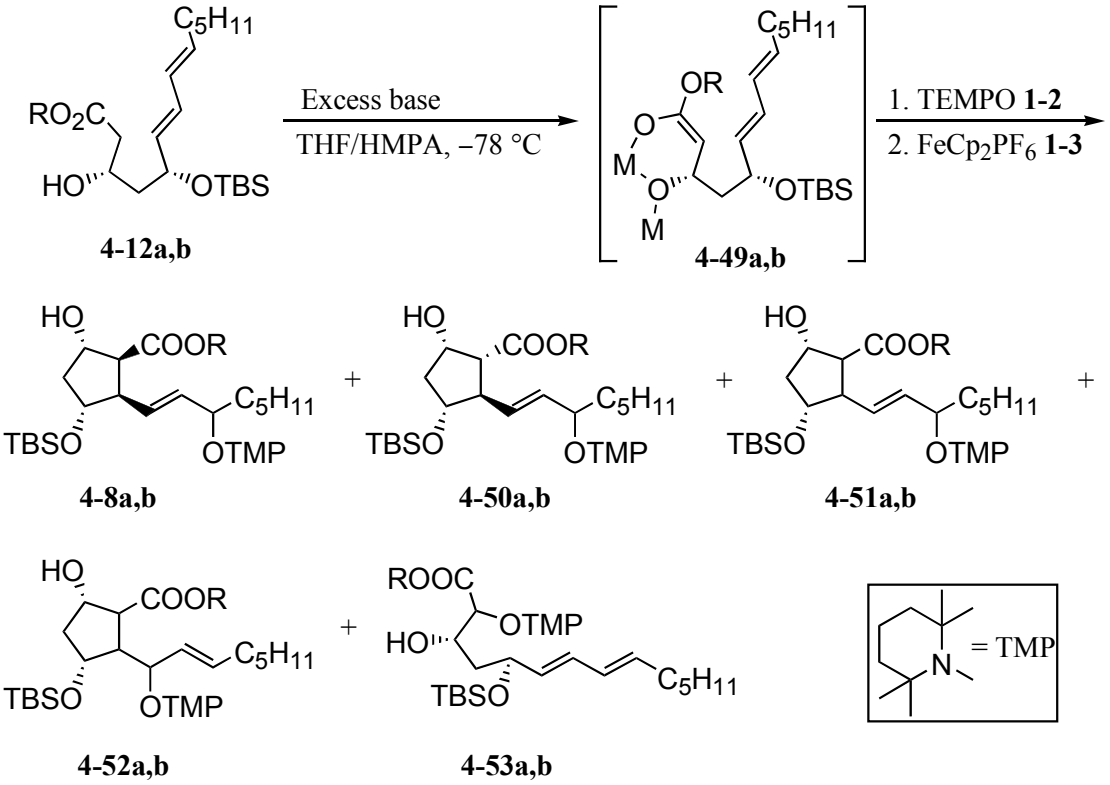


Table 4.11 Cyclisations with different metal ions and **1-2** added after deprotonation

Entry	Substrate	Setup (mmol)/ Equiv. Base/ Additives	**4-12**[a]	**4-8**+**4-50**	**4-8** (α/β): **4-50** (α/β)	**4-52**[b] (%)	**4-53** (%)
1	**4-12a**	0.65/ 2.5 LDA/ 7 LiCl/ 6 HMPA	1	71	1.4(1:1.1): 1(2:1)	1[c]	8
2	**4-12b**	0.7/ 2.5 LDA/ 7 LiCl/ 6 HMPA	13	58	1.1 (1.8:1): 1(1:1.4)	8[d]	-
3	**4-12a**	0.65/ 1.5 *t*BuMgCl/ 2.2 LDA/ 6 HMPA	12	41	1(1:1.1): 4.1(2.1:1)	7[e]	19
4	**4-12b**	0.7/ 1.5 *t*BuMgCl/ 2.2 LDA/ 6 HMPA	23	46	1(1.7:1): 6(1.7:1)	8[f]	17

a) Recovered. b) Four cyclic proximal products isolated; the d.r. is given with increasing polarity. c) d.r. 0:0:1:0; additionally **4-51** was detected in 3% yield. d) d.r. 3:1:3.25:0; additionally **4-51** was detected as trace. e) 2.2:1:0:0; additionally **4-51** was detected in 1% yield. f) d.r. 1.4:1:0:0.

In the cyclisations of the mixed Li/Ti and Li/B alkoxido-enolates generated by deprotonation of **4-12b** with LDA/ClTi(O*i*Pr)$_3$ or of **4-12a** with Et_2BOMe/LDA the substrate was recovered. It was not certain whether the deprotonation of **4-12a,b** occurred (not shown).

The formation of acyclic trapping products **4-53a,b** occurs via a bimolecular coupling reaction of the α-carbonyl radical with TEMPO **1-2** before the radical cyclisation, and it is dependent on the concentration of **1-2**. A series of experiments was designed to assay the impact of TEMPO concentration on the product distribution in the radical cyclisations of **4-12b** (Table 4.12). When TEMPO **1-2** was well mixed with ferrocenium hexafluorophosphate **1-3** and added in portions at –78 °C (Method A, entry 1), the major isomers **4-8b** and **4-50b** were isolated in 57% yield, similar to results in Table 4.11 (*vide supra*). Cyclic products **4-52b** were detected in minute amounts (2% yield). Moreover no acyclic tempo adduct **4-53b** was formed and **4-12b** was recovered in 17% yield. In method B 0.2 equiv. of **1-2** was added before cyclisation and the oxidation was performed using a mixture of 0.8 equiv. **1-2** and 1 equiv. of **1-3**, providing **4-8b** and **4-50b** in lower yield of 45% yield (entry 2). The yield of the cyclic proximal products **4-52b** increased to 13%. A larger amount of **4-12b** (24%) was recovered. When method B was applied at higher oxidation temperatures of –30 °C (Method C, entry 3) 56% of the substrate was recovered and complex mixtures containing **4-8b** and **4-52b** were obtained.

Table 4.12 Oxidative cyclisations of **4-12b** with low concentration of TEMPO

Entry	Method	Setup (mmol)/Equiv. Base/Additives	**4-12b** (%)	**4-8**+**4-50** (%)	**4-8** (α/β):**4-50** (α/β)	**4-52** (%)
1	A[a]	0.7/ 2.5 LDA/ 7 LiCl/ 6 HMPA	17	57	1(2:1): 1(1.05:1)	2[b]
2	B[c]	0.59/ 2.5 LDA/ 8.7 LiCl/ 6 HMPA	24	45	1(2.6:1): 1(1:1.4)	13[d]
3	C[e]	0.59/ 2.5 LDA/ 8.7 LiCl/ 6 HMPA	56	A complex mixture was obtained, containing 15α-IsoP **4-8** and **4-52**.		

a) Method A: **1-2** (1 equiv.) and **1-3** (1 equiv.) were well mixed and added in portions at –78 °C, followed by addition of **1-3** until the reaction remained dark blue. b) d.r. 0:0:1.2:1, the d.r. is given with increasing polarity; additionally **4-51** was detected in 1% yield. c) Method B: A portion of TEMPO (0.2 equiv.) was added before oxidation, and then a mixture of TEMPO (0.9 equiv.) and $FeCp_2PF_6$ (1 equiv.) was added in portions at –78 °C. d) d.r. 3.9:trace:1:1, the d.r. is given with increasing polarity; additionally **4-51** was detected in 3% yield. e) Method C: A portion of TEMPO (0.2 equiv.) was added before oxidation, followed by addition of a mixture of TEMPO (0.8 equiv.) and $FeCp_2PF_6$ (1 equiv.) in portions at –30 °C.

The modified procedures using low concentrations of TEMPO during the oxidation/radical cyclisation did not improve the yields or product distribution for setups below 1 mmol. But method B boosted the efficiency of the cyclisations on scale up (Table 4.13). Deprotonation with 2.5 equiv. of LDA for 1.5 h in the presence of 7 to 15 equiv. of LiCl, subsequent addition of 6 equivalents of HMPA and 0.2 equiv. of TEMPO followed by oxidation with a mixture of 1 equiv. **1-3** and 0.8 equiv. **1-2** afforded 61 to 77% yield of the cyclic products **4-8a,b** and **4-50a,b** (Entries 1, 2, 4 and 5). IsoP **4-8a,b** was produced from **4-12a,b** often in a slight excess over **4-50a,b** (entries 2, 3, 5). Products **4-51** and **4-52** were generally detected in smaller amounts. Deprotonation with only 2.3 equiv. LDA decreased the yield of **4-8b**, **4-50b** and **4-51b** to 52%, while 25% of substrate **4-12b** was recovered (entry 6). A larger excess of LiCl (15 or 25 equiv.) favoured the formation of the acyclic TEMPO adduct **4-53a** (Entries 2 and 3). The diastereoselectivity of the side chain stereocentre in 15-position **4-8** and **4-50** was variable. There was no recognisable correlation pattern between 15α/β-ratios and the ester substitution pattern in **12a,b** or the reaction conditions.

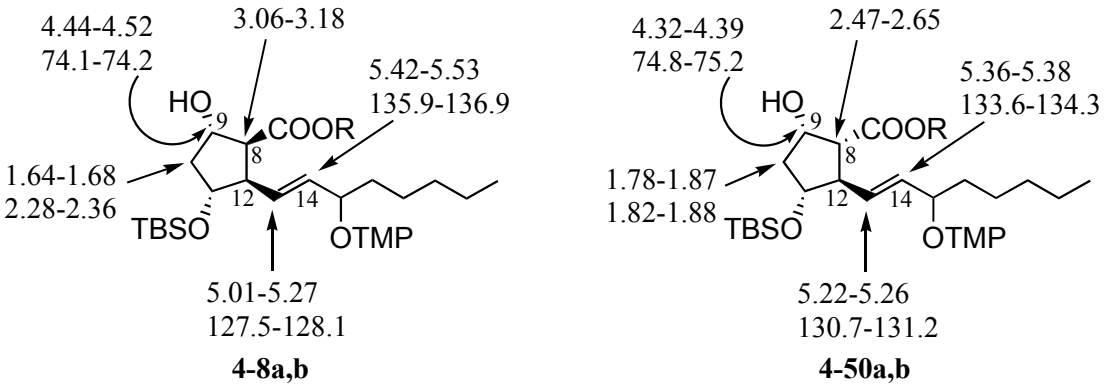
Table 4.13 Scale up experiments[a]

Entry	**4-12**	Setup (mmol)/ Equiv. Base/ Additives	**4-12** (%)	**4-8**+ **4-50**	**4-8** (α/β):**4-50** (α/β)	**4-51** (%)	**4-52**[b] (%)	**4-53** (%)
1	**4-12a**	2.9/ 2.5 LDA/ 7 LiCl/6 HMPA	2	66	-	4	2	1
2	**4-12a**	3.1/ 2.5 LDA/ 15 LiCl/6 HMPA	5	62	1.7(1:1.7):1(3:1)	1	8[c]	7
3	**4-12a**	3.1/ 2.5 LDA/ 25 LiCl/6 HMPA	3	55	1.3(1.4:1):1(1:2.3):1	-	14[d]	10
4	**4-12b**	1.76/2.5 LDA/ 7 LiCl/6HMPA	4	77	1(2.1:1):1.2(1.2:1)	-	14[e]	-
5	**4-12b**	2.4/ 2.5 LDA/ 7 LiCl/6HMPA	1	61	1.3(2.2:1):1(1.2:1)	4	9[f]	-
6	**4-12b**	3.5/2.3 LDA/ 7 LiCl/6 HMPA	25	52	1(1:1.1):1(1:1)	4	6[g]	-

a) A portion of 0.2 equiv. of TEMPO was added before oxidation, and then a mixture of TEMPO (0.9 equiv.) and $FeCp_2PF_6$ (1 equiv.) was added in portions at –78 °C. b) The d.r. is given with increasing polarity. c) d.r. 4.2:1:3.4:2.7. d) d.r. 4.4:1.6:1.8:1. e) d.r. 3.8:1:1.1:trace. f) d.r. 6.7:1:1.5:1. g) d.r. 8.1:1:1:2.2.

The structure of the cyclisation products was established on the basis of their ^{1}H and ^{13}C NMR, COSY and HSQC NMR spectra (Table 6.5, Figure 4.4).

Figure 4.4 Significant chemical shifts of compounds **4-8a,b** and **4-50a,b**



- The ring protons H8 (dd at 3.06-3.18 ppm) in IsoP isomers **4-8a,b** are downfield shifted by 0.55-0.59 ppm compared to the corresponding PG isomers **4-50a,b** (dd at 2.47-2.65 ppm).
- The ring protons H9 are in IsoP isomers **4-8a,b** (m at 4.44-4.52 ppm) downfield shifted by 0.11-0.18 ppm compared to those of the corresponding PG isomers **4-50a,b** (m at 4.32-4.39 ppm). The resonances of the corresponding carbon atoms of IsoP isomers are upfield shifted by 0.7-1.2 ppm compared to the PG isomers **4-50a,b**.
- The protons in the 10-position of IsoP isomers **4-8a,b** displayed two well separated signals at 1.64-1.68 and 2.28-2.36 ppm, respectively, while the H10 signals in PG isomers **4-50a,b** are very close to each other or even overlap at 1.78-1.88 ppm.
- The chemical shift difference of the allylic protons Δ(δH13-δH14) is larger for IsoP-isomers (0.25-0.42 ppm), while Δ(δH13-δH14) of PG-isomers has values in the range 0.13-0.16 ppm. The chemical shift difference δC13-δC14 accounts for 8.0-9.4 ppm in IsoP-isomers **4-8a,b**. In PG-isomers Δ(δC13-δC14) amounts to 2.2-3.1 ppm.

The relative ring configuration of the isoprostane isomers **4-8b** and prostaglandin isomers **4-50b** was proven on the basis of NOE and NOESY experiments. The relative configuration of **4-8a** and **4-50a** was strengthened by comparison with **4-8b** and **4-50b**. The configuration at the exocyclic stereocentre was assigned by comparison with cyclisation products **4-7a,b** and **4-45a,b** and with model compounds.[85]

Key results:

- A cyclisation method for the synthesis of cyclopentane carboxylates **4-8a,b** and **4-50a,b** was developed. The **4-8a,b**/**4-50a,b** diastereoselectivity could be switched by using lithium or magnesium as the counter ions in enolates **4-49a,b**.

- The formation of the cyclic proximal products **4-52a,b** and the acyclic adduct **4-53a,b** as well as the recovery of large amounts of the cyclisation substrates **4-12a,b** in the cyclisations of the mixed Li, Mg-alkoxido enolates were yield limiting processes.
- The reaction was successfully scaled up to gain the material necessary for the accomplishment of the total synthesis. The *tert*-butyl esters **4-8b** and **4-50b** were easier to separate then the methyl esters **4-8a** and **4-50a**.

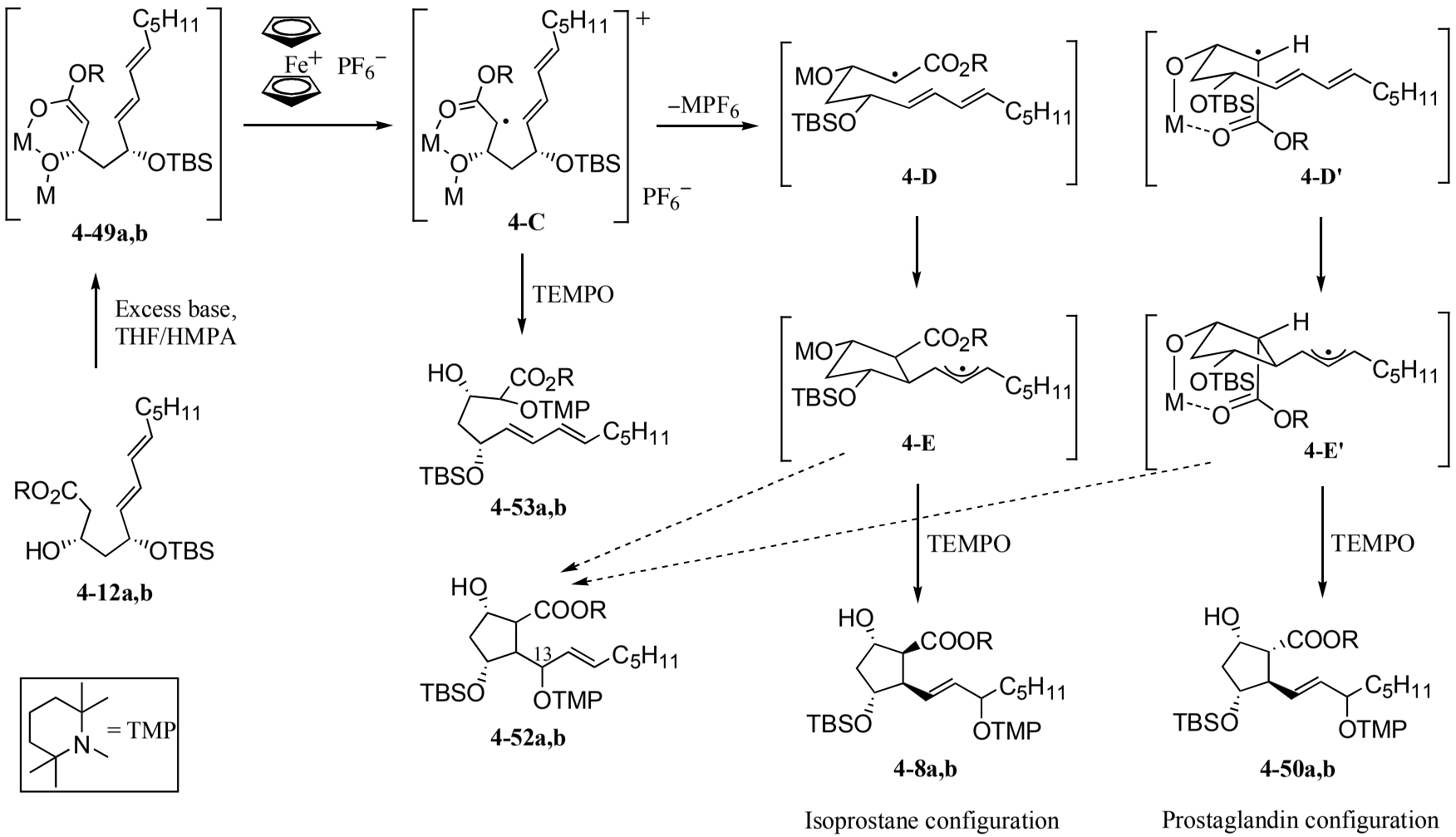
4.4. Mechanistic rationalisation

The control of diastereoselectivity was the decisive point in the investigations of oxidative cyclisations of **4-11a,b** and **4-12a,b** (Scheme 4.19, only **4-12a,b** shown). Dienolates **4-49a,b** generated from hydroxy esters **4-12a,b** were oxidised by ferrocenium hexafluorophosphate **1-3**. Since **1-3** is an outer sphere oxidant the oxidation may occur by initial SET leading to **4-C**, followed by elimination of a metal of MPF_6. Cyclisation of resulting radicals **4-D** and **4-D'**, followed by trapping of allylic radicals **4-E** and **4-E'** with TEMPO furnished a mixture of diastereomers **4-8a,b** and **4-50a,b**, accompanied by small amounts of the regioisomeric products **4-52a,b**, which result from TEMPO trapping at 13-position. Premature coupling of radicals **4-D** and **4-D'** with TEMPO provided acyclic product **4-53a,b**.

The results point to a partial chelation in the transition state of the oxidative cyclisation of enolate **4-49a,b**. The applied metal ion played a significant role. To assemble the isoprostane configurated isomer **4-8a,b**, the cyclisation occurred preferentially via non-chelated transition state **4-D**. Coupling of the resulting radical **4-E** with TEMPO led to **4-8a,b** as the major diastereomer. On the other hand, the isomer **4-50a,b** with prostaglandin configuration was predominetly formed via the chelated six membered ring radical anion **4-D'** and subsequent coupling of TEMPO with allylic radical **4-E'**.

This model is supported by the results. With lithium as metal counterion, the isoprostane isomer **4-8a,b** was obtained via Beckwith-Houk type transition state **4-D** as the major diastereomer in moderate excess. The best diastereomeric ratio amounted to 1.7:1 for **4-8a,b**/**4-50a,b** and 2:1 for **4-7a,b**/**4-45a,b**. From Mg/Li mixed alkoxido enolates **4-49a,b** prostaglandin skeleton **4-50a,b** was formed as the main product of the cyclisation in moderate yields but good diastereoselectivity. The magnesium counterion stabilised the chelated form of radical cation **4-C** and the cyclisation proceeded via transition state **4-D'**.

Scheme 4.19 Mechanistic rationalisation



4.5 Reduction of the ester at the C7-position

Reductions of cyclopentanes **4-7b** and **4-45b** occurred in excellent yields (Scheme 4.20, Table 4.14, entries 1 and 2). When the reaction was scaled up to 350 mg, diol **4-54** was obtained in a moderate yield of 58% (entry 3).

Scheme 4.20 Reduction of esters **4-7b** and **4-45b**

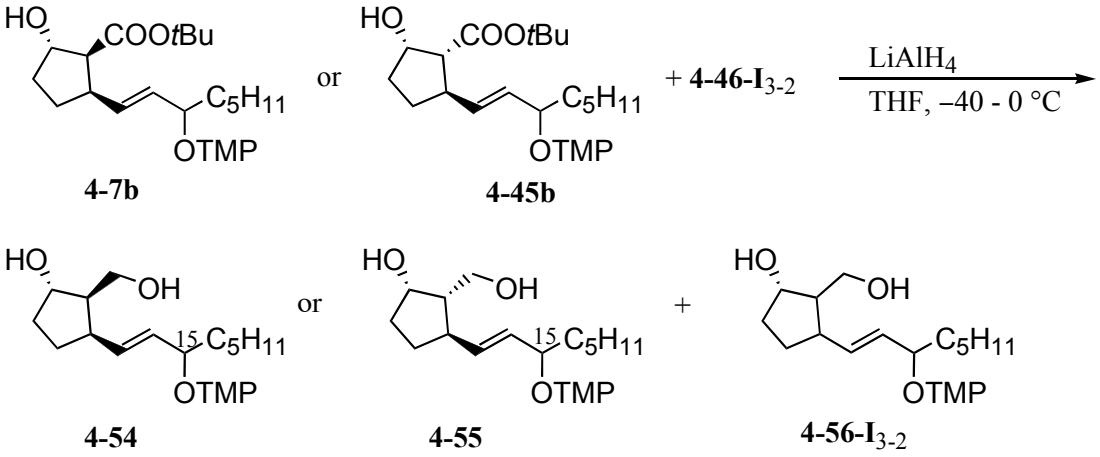


Table 4.14 Reduction of **4-7b** and **4-45b**

Entry	Substrate	Setup mmol	d.r.	Yield (%), d.r.
1	**4-7b**[a]	0.18 (80 mg)	β:α 4.1:1	100 (β-**4-54**:α-**4-54** 4.8:1)
2	**4-45b**	0.15 (70 mg)	α:β 2.25:1	87 (α-**4-55**:β-**4-55** 2.2:1)
3	**4-7b**	0.77 (350 mg)	β:α:**4-46b-I$_{3-2}$** 4.9:1.1:1	58 (β-**4-54**:α-**4-54**:**4-56-I$_{3-2}$**[b] 4.1:1.7:1)

a) This sample contains traces of **4-46b-I$_{3-1}$**. b) The ring configuration was not unambiguously assigned.

The relative ring configuration of diastereomers 15α-**4-54**, 15β-**4-54**, 15α-**4-55** and 15β-**4-55** as well as the configuration of the exocyclic stereocentre was assigned based on the known configuration of the reduction precursors **4-7b** and **4-45b**. The characteristic proton signal of the methylene group at 3.59-3.86 ppm denoted the presence of the hydroxy group (Table 4.15). The corresponding carbon atoms at the same position gave triplets at 61.5-62.7 ppm. The NMR data were similar to those of F_{2t}-diols **4-57** and **4-58**.

Table 4.15 Significant NMR data for structure elucidation of **4-54** and **4-55**

Position	α-**4-54**	β-**4-54**	α-**4-55**	β-**4-55**
	δ (ppm), multiplicity			
CH$_2$OH	3.59, 3.68 (AB of ABX), 62.7 (t)	3.76 (m), 61.5 (t)	3.86 (AB of ABX), 62.2 (t)	3.86 (m), 61.5 (t)
*CH*CH$_2$OH	2.15 (m), 53.2 (d)	2.15 (m), 54.0 (d)	2.03 (m), 52.8 (d)	2.03 (m), 51.6 (d)
CH=CHCHOTMP	5.60 (dd), 133.5 (d)	5.49 (dd), 135.5 (d)	5.48 (dd), 135.2 (d)	5.34 (m), 134.5 (d)
=*CH*CHOTMP	5.38 (ddd), 132.4 (d)	5.43 (m), 133.0 (d)	5.34 (dd), 133.1 (d)	5.34 (m), 133.3 (d)

The ester functionality of sterically more hindered cyclopentanes **4-8a,b** was also transformed to the diols **4-57** via reduction with $LiAlH_4$ (Scheme 4.21). This reaction occurred in yields of 60-89% for the methyl ester **4-8a** (Table 4.16, entries 1, 2, 4, 5 and 7). The reduction of the *tert*-butyl ester **4-8b** was much slower (entries 3 and 6). It was important especially for scale up to use a large excess of $LiAlH_4$, otherwise the reactions were very sluggish. The yields and mass balances were however lower in reactions at larger scales. With milder reagents like DIBAL-H no reaction was observed and the starting material was completely recovered.

IsoP-isomers **4-8a,b** were reduced in better yields than cyclopentanes with PG-configuration **4-50a,b**. This was especially noticeable when the reaction was performed on a mixture of IsoP- and PG-isomers, because an enrichment in the IsoP isomers **4-57** was constantly observed (entries 2, 4, 5 and 7).

The lower yields of *tert*-butyl esters **4-8b** of 20-59% (Table 4.16, only the best results shown) can be traced to their steric hindrance. However, the substrates were recovered only rarely, thus the yield limiting process must be a different one. Often the aldehyde **4-59** and the in 11-position deprotected cyclopentane ester **4-60** were isolated in low yields. Maybe an aluminium salt of the free acid was formed and got lost during the workup. The use of different workup procedures did not change the outcome much.

Scheme 4.21 Reduction of esters **4-8a,b**

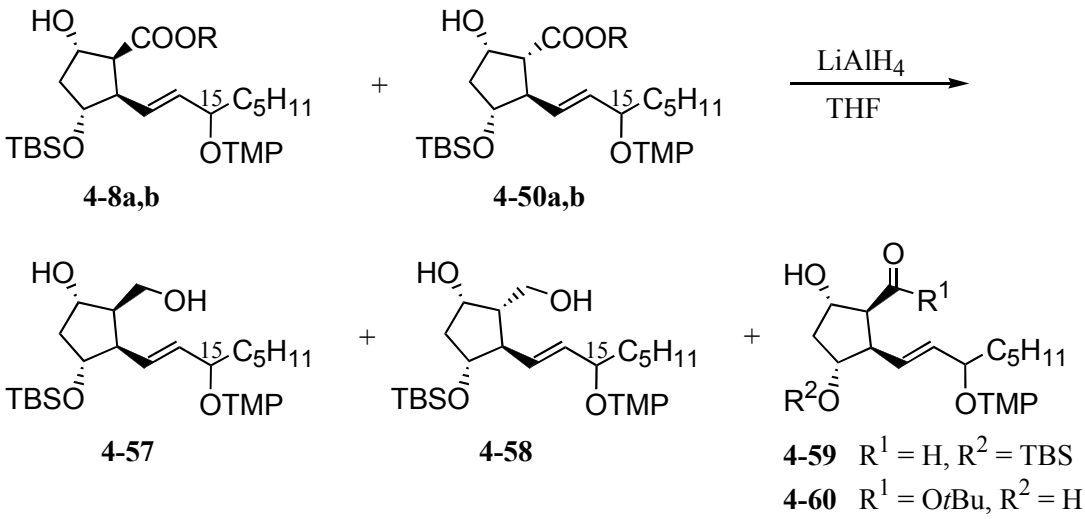


Table 4.16 Reduction of esters **4-8a,b** and **4-50a,b**

Entry	Substrate	d.r.[a]	Setup (mmol)	Workup[b]	**4-57**+**4-58** (d.r.)[c]
1	**4-8a**	0:1:0:0	0.11	A	89% (0:1:0:0)
2	**4-8a/4-50a**	2.8:10:14:1	0.24	A	65% (0:1.5:1:0)
3	**4-8b**	5.5:1:0:0	0.48	B	53% (5:1:0:0)[d]
4	**4-8a/4-50a**	6.1:3.3:3.6:1	0.39	C	60% (2.5:1.4:1:0)
5	**4-8a/4-50a**	6.1:3.3:3.6:1	0.37	C	79% (3.8:1.5:1:0)
6	**4-8b/4-50a**	7:4:2:0	0.40	C	59% (1.5:1:0:0)
7	**4-8a/4-50a**	3.9:2.4:2.4:1	0.25	D	62% (6.2:5:1:0)

a) d.r. at the 15-position = 15α-**4-8**:15β-**4-8**:15α-**4-50**:15β-**4-50**. b) The methods are described in the experimental part. c) d.r. at the 15-position = 15α-**4-57**:15β-**4-57**:15α-**4-58**:15β-**4-58**. d) Additionally **4-59** 16%, **4-60** 8% were isolated.

The relative ring configuration of diastereomers 15α-**4-57**, 15β-**4-57** and 15α-**4-58** as well as the configuration of the exocyclic stereocentre was assigned based on the known configuration of the reduction precursors. The IsoP ring configuration of 15α-**4-57** and 15β-**4-57** was additionally confirmed by NOESY experiments.

The following NMR data were significant for the assignment of the structure of diols **4-57** and **4-58** (Table 4.17): The protons of the methylene group bearing the hydroxy function appeared as the AB part of an ABX system at 3.61-3.80 ppm; the resonances of the ring protons in 8-position of 15α-**4-57** and 15β-**4-57** appeared at 2.36 ppm and at 2.44 ppm, respectively. The shifts of the same proton in 15α-**4-58** differed significantly, being upfield shifted by 0.52 ppm. In the ^{13}C NMR spectra, the methine carbon bearing the hydroxymethyl

group gave a characteristic doublet at 52.0-53.6 ppm. The vinylic carbon atoms absorbed in the range 129.8-135.3 ppm. The difference of the chemical shifts Δ(δC14-δC13) was larger for the IsoP-isomers **4-57** (3-4.9 ppm) than for the PG-isomer 15α-**4-58** (1.4 ppm).

Table 4.17 Significant NMR data of **4-57** and **4-58**

Position	15α-**4-57**	15β-**4-57**	15α-**4-58**
	δ (ppm), multiplicity		
CH$_2$OH	3.61 (AB of ABX), 62.9 (t)	3.69,[a] 3.76,[a] 61.4 (t)	3.80 (m), 62.4 (t)
*CH*CH$_2$OH	2.36 (m), 52.6 (d)	2.44 (m), 53.6 (d)	1.82 (m), 52.0 (d)
CH=CHCHOTMP	5.27 (dd), 129.8 (d)	5.28 (dd), 132.5 (d)	5.23 (dd), 132.8 (d)
=*CH*CHOTMP	5.44 (ddd), 134.7 (d)	5.51 (m), 135.3 (d)	5.41 (dd), 134.2 (d)

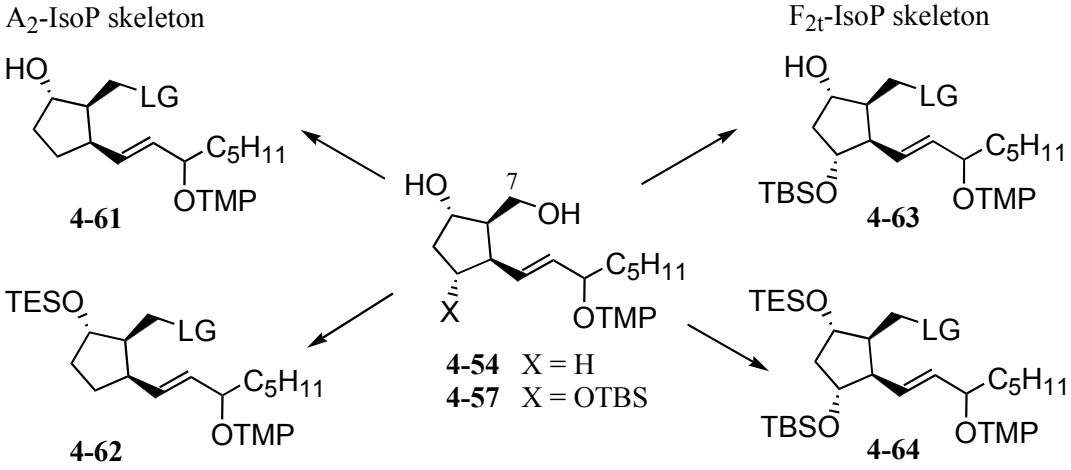
a) A and B parts of ABX.

Key results: Cyclopentane carboxylates **4-7b** and **4-45b** were reduced in high yields at small scales. Introduction of the additional silyloxy group in **4-8a,b** and **4-50a,b** apparently changes the conformation of the ring, so that reduction became significantly more difficult, especially for PG isomers **4-50a,b**. With all substrates the yield dropped on scale up.

4.6. Transformation of the primary hydroxy group in diols 4-54 and 4-57 to a leaving group

The introduction of different leaving groups in 7-position leading to compounds **4-61**-**4-64** was studied next (Scheme 4.22).

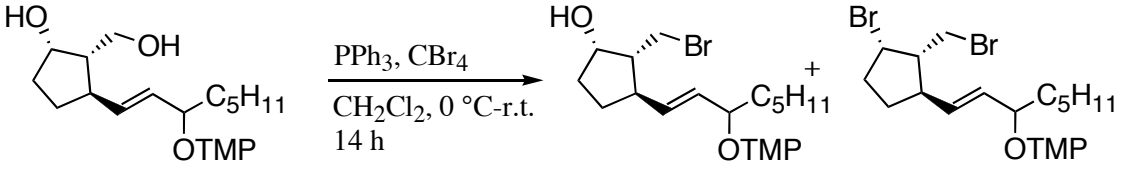
Scheme 4.22 Introduction of leaving groups in 7-position of diols **4-54** and **4-57**



Orienting bromination experiments with alcohol **4-54** using CBr_4 and PPh_3 in CH_2Cl_2 led mainly to decomposition.[147] A similar experiment with the PG-configurated alcohol **4-55**

afforded bromide **4-65** in moderate yield of 51% (Scheme 4.23). In addition, dibromide **4-66** was obtained in 30% yield. It was thus necessary to find more efficient transformations of the primary alcohol into a leaving group, which is also applicable for **4-54** with IsoP-configuration.

Scheme 4.23 Bromination of **4-55**



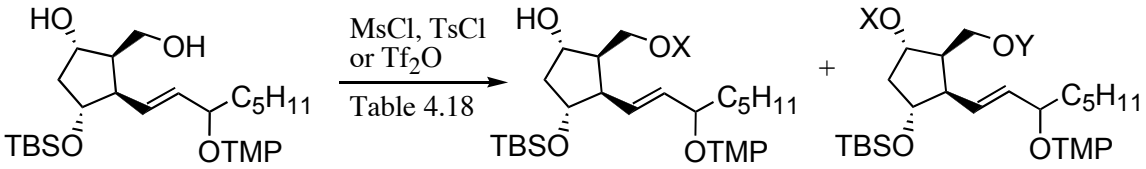
4-55 **4-65** 51% **4-66** 30%

The monosulfonylation of diols **4-57** appeared to be a promising alternative. The mesylation of the diol **4-57** with 1.1 equiv. MsCl and 2 equivalents of NEt_3 afforded 48% of **4-67a**, 35% of the dimesylated product **4-68a**, and even some product **4-69a** mesylated in 9-position (Scheme 4.24, Table 4.18, entry 1). An attempt to optimise this reaction by using only 0.95 equivalents of MsCl at lower temperature showed that the primary as well as the secondary alcohol groups were reactive in this sulfonylation reaction (entry 2). The selectivity for **4-67a** over **4-68a** was higher, but the overall conversion decreased and more of the secondary monosulfonate **4-69a** was isolated.

A sterically more demanding sulfonyl group was expected to differentiate better between the secondary and the primary alcohol functions in **4-57**. A set of experiments with TsCl[148] under different conditions afforded product **4-67b**, however, in poor yields, accompanied by variable amounts of **4-68b** and **4-69b** (entries 3, 4 and 5).

The sulfonylation of **4-57** with triflic anhydride provided **4-67c** in a moderate yield of 40% (Table 4.18, entry 6). Products **4-68c** or **4-69c** were not detected. Although the yield was not satisfactory, the more reactive sulfonylating group reacted more selectively with the primary hydroxy group.

Scheme 4.24 Sulfonylation of diol **4-57**



4-57

4-67a X = Ms
4-67b X = Ts
4-67c X = Tf

4-68a X = Y = Ms
4-69a X = Ms, Y = H
4-68b X = Y = Ts
4-69b X = Ts, Y = H

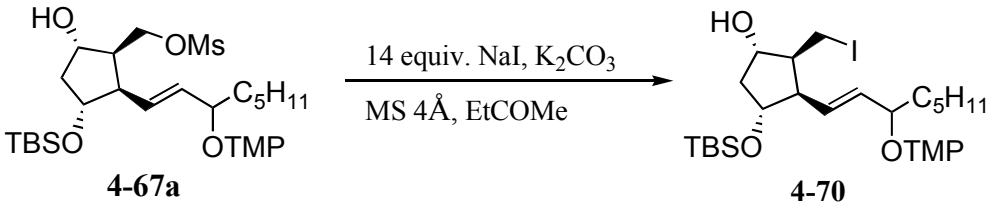
Table 4.18 Sulfonylation Reactions

Entry	X	15-Pos. Config.	**4-67** (%)	**4-68** (%)	**4-69** (%)	**4-57** (%)
1[a]	Ms	α:β 3.07:1	48 (α:β 3.8:1)	35 (α:β 5.3:1)	7 (α:β 1:1)	7 (α:β 1:2)
2[b]	Ms	α	34	9	17	34
3[c]	Ts	α	25	-	5	67
4[d]	Ts	α	15	10	3	28
5[e]	Ts	α	19	47	-	12
6[f]	Tf	α	40	0	-	28

a) 1.1 equiv. MsCl, 2 equiv. Et_3N/–20 °C. b) 0.94 equiv. MsCl, 2 equiv. Et_3N/–50 °C. c) 1.06 equiv. TsCl, 4.2 equiv. Et_3N/–80 - 0 °C. d) 1.06 equiv. TsCl, 2 equiv. Et_3N/0 °C. e) 1.3 equiv. TsCl, 1.8 equiv. Et_3N/ r.t., after 28 h another 0.8 equiv. TsCl and 1.8 equiv. Et_3N were added. f) 1 equiv. Tf_2O, 3.2 equiv. 2,6-lutidine/–78 °C.

The mesylate **4-67a** was converted into the more reactive iodide **4-70** in 86% yield, via a Finkelstein reaction employing NaI and K_2CO_3 in the presence of molecular sieves 4Å in ethyl methyl ketone (Scheme 4.25).

Scheme 4.25 Finkelstein reaction of mesylate **4-67a**



4-67a **4-70**

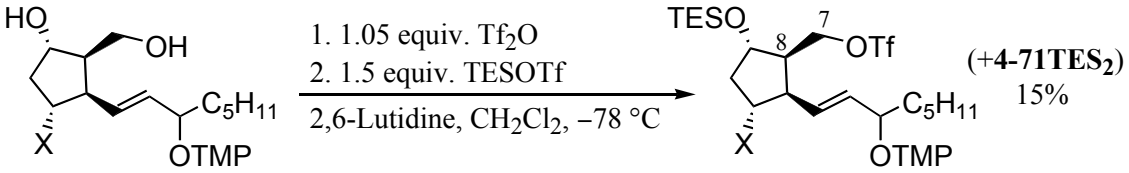
The protons of the methylene group bearing the sulfonyl group and the ring proton in 2-position in compounds **4-67a-c** are downfield shifted compared to the diol precursors (Table 4.19). Similar trends were observed for the chemical shifts of the carbon atoms bearing the sulfonyl group. In contrast, the same position in the iodide **4-70** was upfield shifted to 2.91 ppm (^{1}H NMR) and 6.2 ppm (^{13}C NMR), respectively.

Table 4.19 Significant NMR data for structure assignment of **4-67a-c** and **4-70**

	4-67a δ (ppm), multiplicity	**4-70**	**4-67b**	**4-67c**
*CH_2*X	4.08, 4.16 (AB of ABX), 69.8 (t)	2.91 (t), 6.2 (t)	3.88-4.06 (m), 70.4 (t)	4.44 (d), 77.0 (t)
*C*HCH_2X	2.59 (m), 50.0 (d)	2.63 (m), 53.7 (d)	2.49 (m), 49.9 (d)	2.67 (dq), 50.3 (d)

Since the sulfonylation with triflic anhydride proceeded selectively and subsequent investigations of the alkylation reactions showed that the protection of the hydroxy group in 9-position is very important (*vide infra*), a simultaneous activation/protection sequence was developed. Therefore diols **4-54** and **4-57** were treated successively with fresh triflic anhydride and triethylsilyl triflate in the presence of 2,6-lutidine (Scheme 4.26).[149] Compound **4-71** was isolated in 47% yield in an inseparable mixture with 15% yield of the bis-triethylsilylated diol **4-71TES$_2$** (see Experimental part). Triflate **4-73** was obtained in 81% yield. This reaction proceeded selectively only with fresh triflic anhydride, otherwise inseparable mixtures **4-73** and **4-73TES$_2$** (not shown) were isolated.

Scheme 4.26 Selective sulfonylation of diols **4-54** and **4-57**



X = H **15-α/β-4-54/4–56–I$_{3-2}$** 4.1:1.7:1 — 47% **15-α/β-4-71/4-72-I$_{3-2}$** 5:1:trace

X = OTBS **15-α/β-4-57** 1:1.4 — 81% **15-α/β-4-73** 1:1.2

15-α/β-4-57 1:1.3 — 80% **15-α/β-4-73** 1:1

The assignment of the structures was performed by their NMR data (Table 4.20). The protons in 7-position displayed downfield-shifted signals compared to their precursors, due to the strong electron withdrawing substituent (entry 1). The proton at the 8-position absorbed at 2.22 ppm in **15α-71**, at 2.62 in **15α-73** and at 2.70 ppm in **15β-73** (entry 2). In ^{13}C NMR, the chemical shift of the carbon atoms bearing the triflate unit appeared at 77.1-77.3 ppm, i.e. downfield-shifted compared to precursors **4-54** and **4-57**.

Table 4.20 Significant NMR data of compounds **4-71** and **4-73**

Entry		**15α-4-71** δ (ppm), multiplicity	**15α-4-73**	**15β-4-73**
1	*CH$_2$*OTf	4.27 (m), 4.49 (dd), 77.3 (t)	4.51, 4.60 (AB of ABX), 77.3 (t)	4.44 (m), 77.1 (t)
2	*CH*CH$_2$OTf	2.22 (m), 52.0 (d)	2.62 (dq), 50.4 (d)	2.70 (quint), 50.1 (d)
3	*CH*OTES	3.98 (dd), 74.7 (d)	4.01 (dt), 72.9 (d)	3.91 (m), 73.1 (d)

Key results: The hydroxy group at 7-position of **4-57** is apparently sterically hindered and therefore sulfonylation at the 9-position competed with sterically more demanding sulfonyl groups like the tosyl group. A reasonable selectivity was achieved with small, highly reactive sulfonylation reagents like triflic anhydride.

4.7. Completion of the full carbon atom skeleton of 15-A_2-IsoP and 15-F_{2t}-IsoP via alkylation reactions

The assembly of the full carbon atom skeleton was designed via acetylide alkylation between C6 and C7 - a new strategy in IsoP synthesis. When triflate **4-71** was treated with 2 equivalents of the lithium acetylide **4-9Li** in THF/HMPA at –78 °C, compound **4-5** with the complete 20 carbon atom chain was formed in 29% yield (Scheme 4.27). The derivative **4-6a** (15α/β 1:1.6) was similarly synthesised by alkylation of the triflate **4-73** (15α/β 1:2.1) with **4-9Li** in 71% yield. Some migration of the triethylsilyl group affording triethylsilylalkyne **4-74** was observed. Both main products **4-5** and **4-6a** could not be separated from excess **4-9** and **4-74**. Thus, at this stage both and **4-5** and **4-6a** were further used as a mixture in the following reaction step.

Scheme 4.27 C6-C7 connection via acetylide alkylation of triflates **4-71** and **4-73** with **4-9**

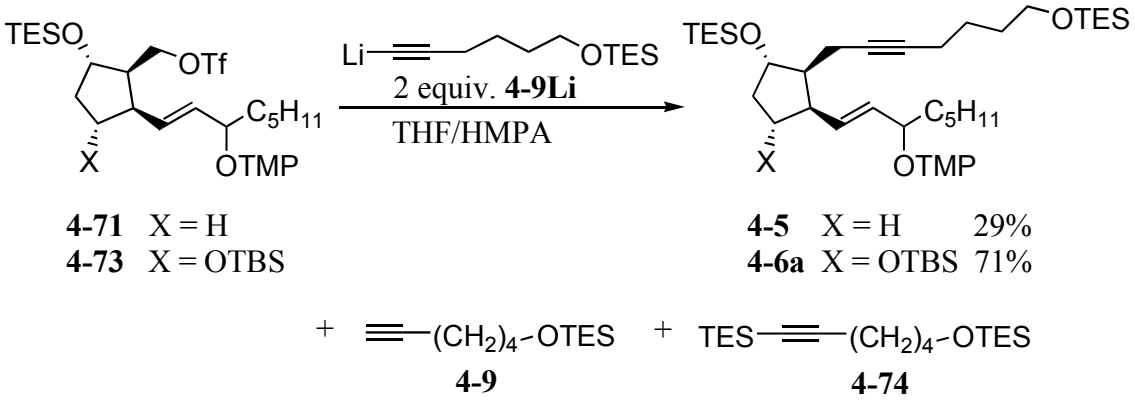


Table 4.21 Significant NMR data of compounds **4-5** and **4-6a**

	α-**4-5**	α-**4-6a**	β-**4-6b**
	δ (ppm), multiplicity		
CH*CH*$_2$C≡	2.14-2.41 (m), 19.1 (t)	2.20-2.48 (m), 19.0 (t)	2.02 (m), 19.1 (t)
C≡*C*	-, 79.8 (s), 80.8 (s)	-, 79.7 (s), 80.8 (s)	-, 80.1 (s), 81.1 (s)
*CH*OTMP	4.26 (m), 85.9 (d)	4.17 (m), 85.8 (d)	4.17 (m), 85.4 (d)
CH=*CH*	5.55 (m), 132.9 (d)	5.30 (dd), 129.8 (d)	5.49 (m), 131.6 (d)
	5.55 (m), 134.4 (d)	5.58 (m), 136.3 (d)	5.49 (m), 136.0 (d)

The structure elucidation was accomplished by means of NMR data (Table 4.21). Two singlets at 79.7-81.1 ppm in the ^{13}C NMR spectra for each of the products attested the formation of an internal alkyne.

Assembly of the carboxylate function early in the synthesis was worthwhile. Accordingly, protection of 5-hexynoic acid as an orthoester **4-10** was carried out (Scheme 4.28).[150] Compound **4-6b** was obtained in 50 to 59% yield in three alkylation experiments of **4-73** with **4-10Li** under slightly different conditions (Table 4.22, entries 1-3). The migration of the triethylsilyl group was also a yield limiting process. Byproduct **4-75** with a free hydroxy group in 9-position was isolated in 26% yield (entry 1). When the reaction time was reduced, product **4-6b** was formed in 54% and 59% yield respectively, but **4-75** was not isolated (entries 2, 3). To avoid losses by hydrolysis of the very acid sensitive OBO ester, the eluent for chromatography had to be slightly basic containing Et_3N.

Scheme 4.28 Alkylation of triflate **4-73** with OBO ester **4-10**

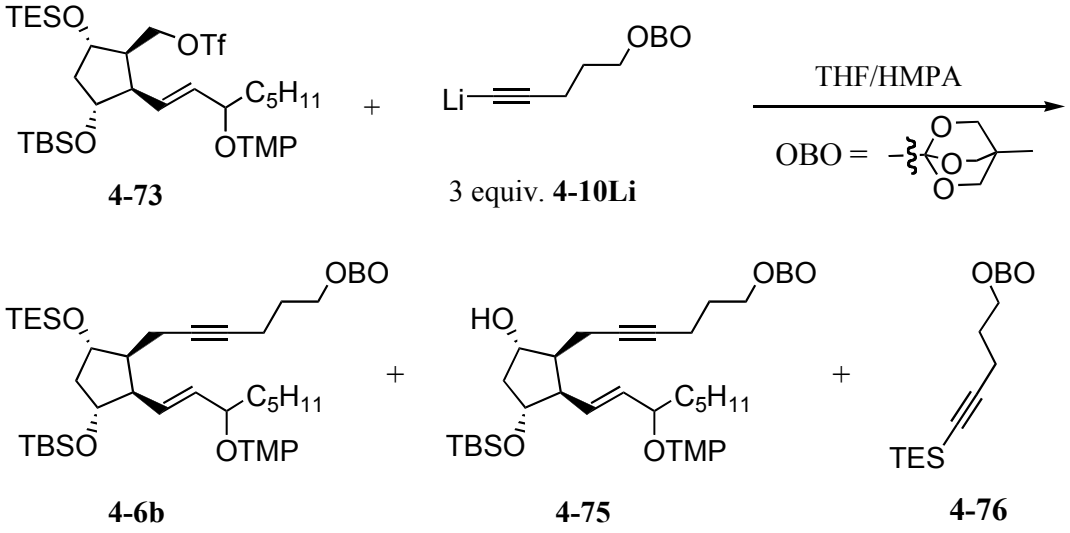


Table 4.22 Alkylation experiments of triflate **4-73** with **4-10**

Entry	Conditions	**4-6b** (%, d.r.)	**4-75** (%)
1[a]	2 h 40 min, –78 °C - –15 °C	50 (15α/β 1:1.6)	26 (15α/β 1:1.2)
2[b]	2 h, –78 °C - –15 °C	54 (15α/β 1.2:1)	-
3[a]	35 min, –78 °C - –55 °C	59 (15α/β 1:1.1)	-
4[a]	2 h 40 min –78 °C - –15 °C, then 2.5 equiv. TESCl	30 (15α/β 1:1)	-

a) From **4-73** 15α/β 1:1.2. b) From **4-73** 15α/β 1:1.

It was assumed that the triethylsilyloxy group in the 9-position exchanged the TES-group with **4-10Li** and that the so formed lithium alkoxide could be reprotected in situ with TESCl. Hence triethylsilyl chloride was added after the alkylation was complete by TLC (entry 4). Unfortunately there was no improvement of the reaction, since **4-6b** was obtained in only 30% yield.

The structures of the products were elucidated based on NMR experiments. The methylene group in 7-position absorbed at 2.18 ppm for **4-6b** and at 2.05 ppm for **4-75**, respectively, in ^{1}H NMR (Table 4.23, entry 1). In ^{13}C NMR this position gave a triplet at 19.0-19.7 ppm. For each isomer two singlets at 79.7-81.6 ppm attested the alkyne. Characteristic chemical shifts of the OBO ester were present in all 4 isomers (Figure 4.5).

Figure 4.5 Significant chemical shifts of the OBO ester units

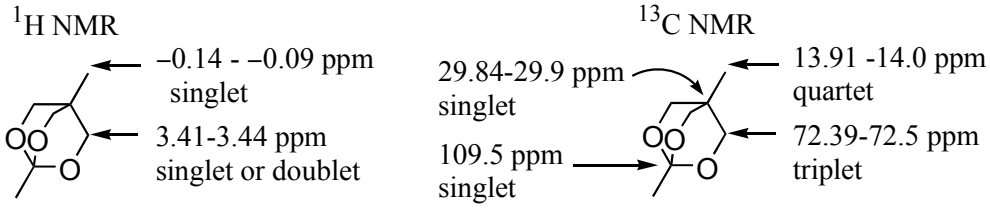
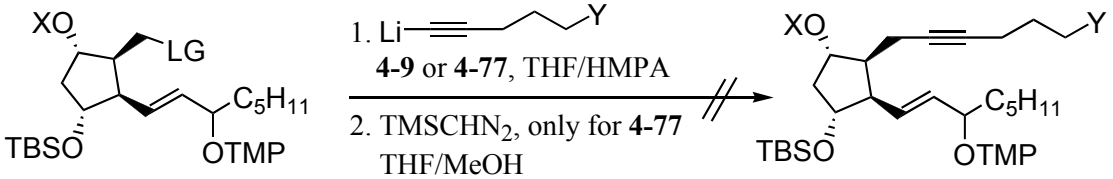


Table 4.23 Significant NMR data of compounds **4-6b** and **4-75**

	4-6b-Isomer 1 δ (ppm), multiplicity	**4-6b**-Isomer 2	**4-75**-Isomer 1	**4-75**-Isomer 2
CH*CH*$_2$C≡	2.18 (m), 19.1 (t)	2.18 (m), 19.0 (t)	2.05 (m), 19.6 (t)	2.05 (m), 19.7 (t)
C≡*C*	80.1 (s), 81.4 (s)	79.7 (s), 81.0 (s)	79.9 (s), 81.3 (s)	80.2 (s), 81.6 (s)
*CH*OTMP	4.18 (m), 85.3 (d)	4.18 (m), 85.9 (d)	4.09 (m), 85.8 (d)	4.14 (m), 85.2 (d)

Scheme 4.29 Alkyation experiments with different substrates



4-70 X = H, LG = I
4-67c X = H, LG = OTf
4-73 X = TES, LG = OTf

4-77 Y = COOLi
4-9 Y = CH_2OTES
4-77 Y = COOLi

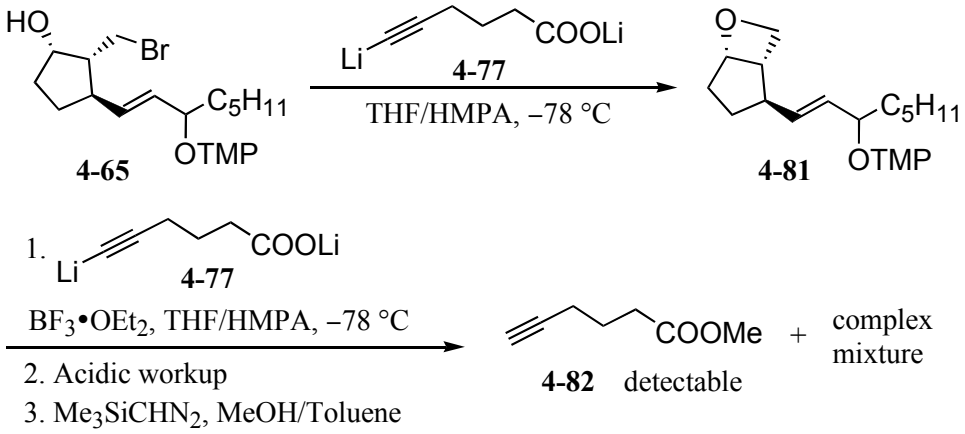
4-78 Y = COOMe
4-79 Y = CH_2OTES
4-80 Y = COOMe

Structural elements of the alkylation substrates were varied. The alkylation of **4-70** having a free hydroxy group with excess of lithium acetylide of 5-hexynoic acid **4-77** and subsequent treatment with $TMSCHN_2$ afforded a complex mixture based on the NMR spectra (Scheme 4.29). An attempt to introduce the C1-C6 unit as **4-9** in triflate **4-67c** also furnished a

complex mixture. When protected **4-73** was treated with the dianion of hexynoic acid **4-77**, followed by esterification with trimethylsilyldiazomethane, traces of compound **4-80** were detected in the NMR spectra of the isolated complex mixture.

Alkylation of bromide **4-65** with an excess of the dianion of 5-hexynoic acid **4-77** afforded surprisingly the oxetane **4-81** in 82% yield (Scheme 4.30). The chemical shifts of the ABX system at 4.13 ppm and 4.78 ppm in the ^{1}H NMR spectrum, as well as the triplet at 74.4 ppm in the ^{13}C NMR spectrum, which were clearly different from the substrate, were assigned to the *CH*$_2$O group. Deprotonation of the hydroxy group in **4-65** by the excess of lithium acetylide and subsequent intramolecular etherification explains the formation of **4-81**. Oxetane **4-81** was treated with the dianion of **4-77** in the presence of boron trifluoride $BF_3{\cdot}OEt_2$, followed by acidic workup and esterification with trimethylsilyldiazomethane. The NMR spectra showed that decomposition occurred, and contained the resonances of **4-82.**

Scheme 4.30 Formation and attempted alkylation of oxetane **4-81**

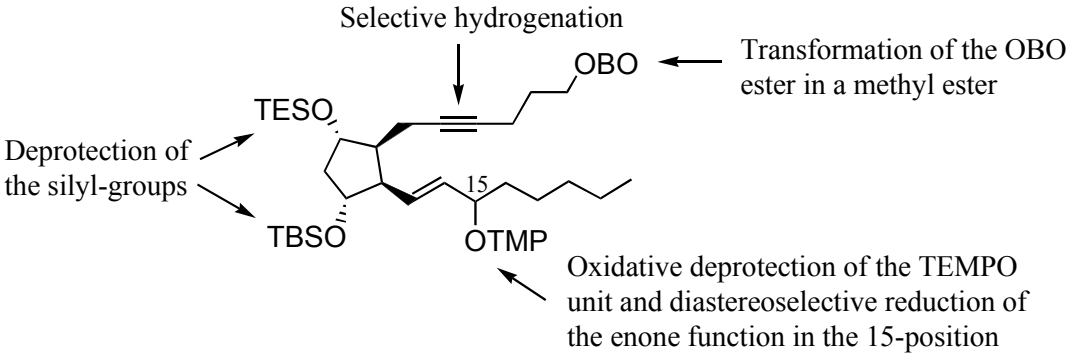


Key results: The completion of the 20-carbon atom skeletons **4-5** and **4-6a,b** was achieved via a S_N2 alkylation reaction. This connection of the C6-C7 carbon atoms is a new strategy in IsoP-synthesis. The protection of the carboxyl function in 5-hexynoic acid **4-77** as well as of the hydroxy group in 9-position in **4-71** and **4-73** were essential for the success of the alkylation reaction.

4.8. Completion of the total synthesis 15-F$_{2t}$-isoprostane

The final steps in the total synthesis of 15-F_{2t}-Isoprostane required the adjustment of functional groups (Figure 4.6). The order of transformations had to be optimised. The selective hydrogenation of the alkyne was planned as the last step, to avoid possible isomerisation of the 5,6-(*Z*)-double bond.

Figure 4.6 Necessary steps for the completion of the total syntheses



4.8.1. Studies towards the oxidative deprotection of the TMP group

Precedence for the oxidative cleavage of (2,2,6,6-tetramethylpiperidinyloxy)alkanes with *m*CPBA exists to obtain aldehydes and ketones.[151] This method was first adapted for the oxidative deprotection of the tetramethylpiperidine unit in cyclopentanes **4-8a,b** and **4-50b** (Scheme 4.31). An important aspect to consider was the susceptibility to epimerisation at the 12-position. Treatment of mixtures of **4-8a,b** with IsoP-configuration and **4-50a,b** with PG-configuration afforded ketones **4-83** and **4-84** in high yields (Table 4.24, entries 1,2). A new isomer **4-85** (12-*epi*-**4-83**) was isolated, interestingly only from IsoP/PG mixtures (entries 1 and 2). The change of diastereomers ratio of products indicated that **4-8a,b** with IsoP-configuration epimerised in 12-position. When the reaction was performed with pure **4-50b**, only traces of a new ketone were detected in the NMR spectrum. Therefore the relative configuration for **4-85** (12-*epi*-**4-83**) in the 8-position was assigned *S**, since this compound originated from **4-8a,b**. In one experiment the product **4-86** resulting from dehydration in 11,12-positions was also detected in 5% yield (entry 2).

Scheme 4.31 Oxidative removal of the TMP-group

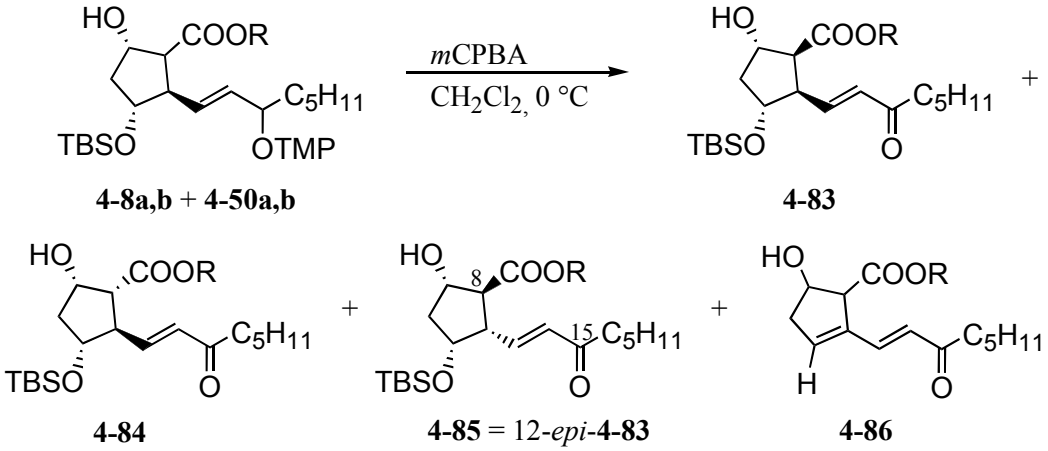


Table 4.24 Oxidative removal of the TMP-group in cyclopentane derivatives **4-8** and **4-50**

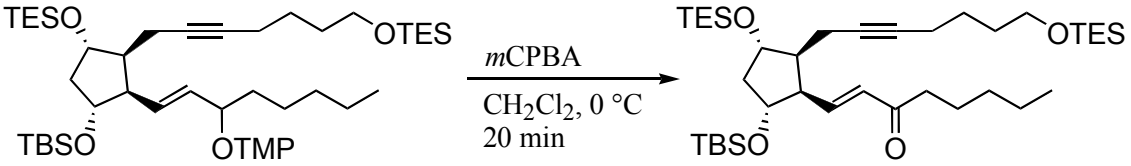
Entry	Substrate	Time (min)	Product (IsoP:PG:12-*epi*-IsoP)	Yield (%)
1	**4-8a**:**4-50a**:**4-51a** (13.3:8.3:1)	30	**4-83a:4-84a:4:85a** (4.3:4.5:1)	73
2	**4-8b**:**4-50b**:**4-52b** (20:26:1)	55	**4-83b:4-84b:4:85b** (3.5:9.6:1)	73[a]
3	**4-50b**	50	**4-84b**	94[b]

a) **4-86** and another unknown isomer were isolated in 5% and 15 % yield, respectively. b) The product contains traces of an unknown isomer.

4.8.2. Oxidative deprotection of the TMP group of compounds 4-6a,b and removal of the silyl groups

The tetramethylpiperidine group of **4-6a** was oxidatively removed with *m*CPBA in high yield (Scheme 4.32). The reaction time was kept short (20 min). Under these conditions only trace amounts of two other isomers were detected based on the signals of an α,β-unsaturated ketone unit in the ^{1}H NMR spectra. Thus **4-87** displayed more resistance to epimerisation. The reaction time proved also to be important. It has to be kept as short as possible.

Scheme 4.32 Oxidative removal of the TMP-group in derivative **4-6a**

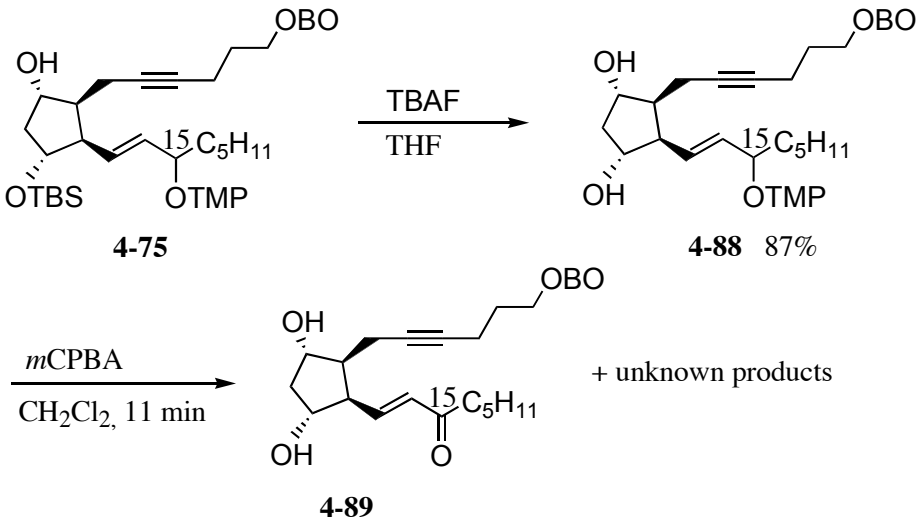


4-6a **4-87** 70%

The deprotection of the silyl group in compound **4-75** (15α/β 1:1.2) with TBAF in dry THF afforded diol **4-88** in 87% yield (Scheme 4.33). Treatment of **4-88** with *m*CPBA provided a crude mixture containing three major components. One of them was the desired product **4-89**, which was unambiguously assigned based on its NMR data (Figure 4.7). The second product displayed a dd at 6.74 ppm and a doublet at 6.12 ppm in the ^{1}H NMR, and is thus also an enone whose structure could not be established. The third also unknown compound had a triplet at 6.87 ppm and a doublet at 8.30 ppm in the ^{1}H NMR spectra. Moreover two other unknown isomers were detected in very small amounts, each of them displayed a doublet at 6.27 and 6.32 ppm respectively in the ^{1}H NMR spectra. Resonances at 173.6 and 171.6 ppm in the ^{13}C NMR spectra indicated that two of these products are (2,2-bis(hydroxymethyl))propyl esters resulting from premature hydrolysis of the OBO-ester

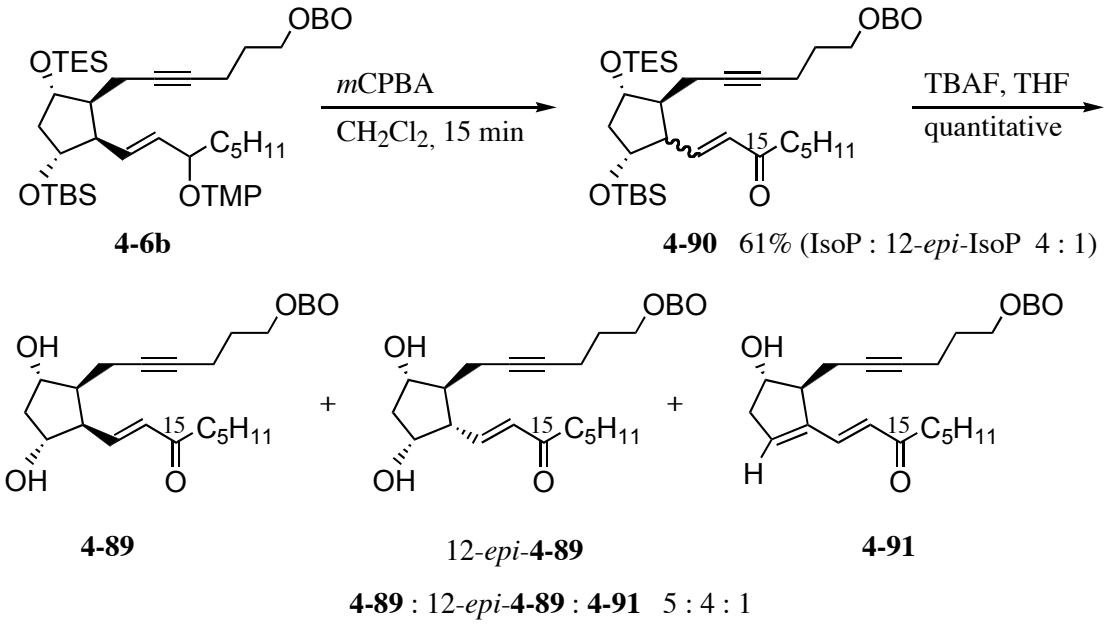
induced by the acidic deprotection conditions (not shown). Product **4-89** decomposed during purification on silica gel.

Scheme 4.33 Synthesis of enone **4-89** from **4-75**



Initial deprotection of the TMP-group in **4-6b** (15α/β 1:1.6) furnished the 15-enone **4-90** in 61% yield**.** Epimerisation at the 12-position of **4-90** occurred during workup and purification affording **4-90** and 12-*epi*-**4-90** in a 4:1 ratio.

Scheme 4.34 Synthesis of enone **4-89** form **4-6b**

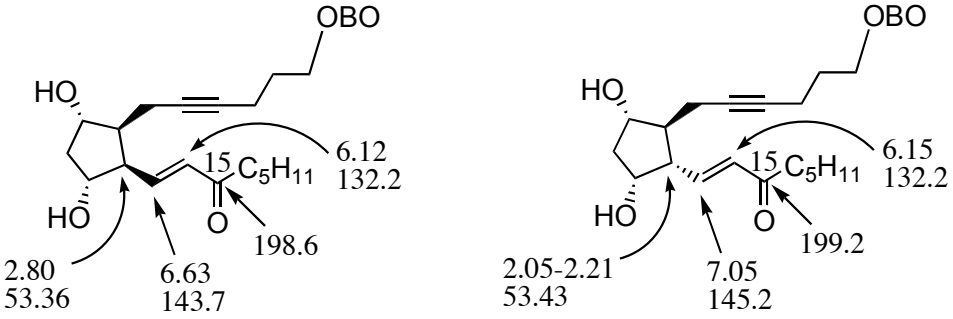


Deprotection of the silyl groups in **4-90** and 12-*epi*-**4-90** with TBAF occurred quantitatively, but epimerisation of **4-89** to 12-*epi*-**4-89** as well as dehydration in 11,12-

position afforded a mixture of three products **4-89**, 12-*epi*-**4-89** and **4-91** in a ratio 5:4:1. A fourth unassigned component was detected in trace amounts. Since epimerisation of the 12-position and competing ring opening of the OBO ester were facile, the oxidative deprotection step in 15-position had to be postponed to one of the last steps.

The enone **4-89** displayed a doublet of doublets at 6.63 ppm and a doublet at 6.12 ppm in the ^{1}H NMR spectrum. 12-*epi*-**4-89** displayed a similar pattern, but H12 appeared significantly downfield-shifted (Figure 4.7).

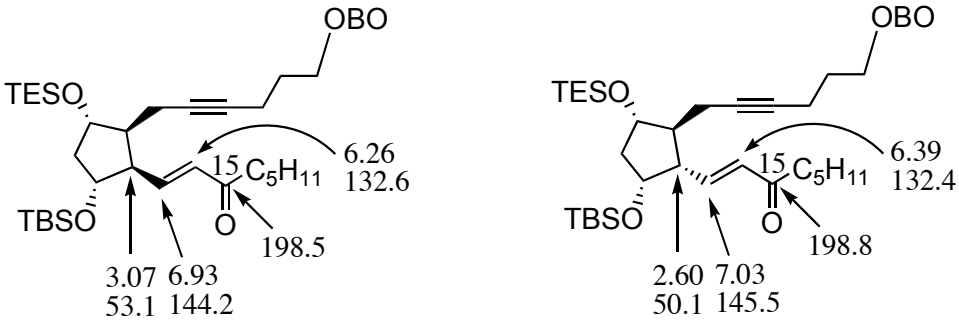
Figure 4.7 Significant ^{1}H and ^{13}C chemical shifts of compounds **4-89** and 12-*epi*-**4-89**



4-89 12-*epi*-**4-89**

In compound **4-90** the protons of the double bond absorb at 6.93 and 6.26 ppm, respectively (Figure 4.8). The carbon atoms of the double bond gave two doublets at 144.2 and 132.6 ppm in ^{13}C NMR, and the ketone appeared as a singlet at 198.5 ppm.

Figure 4.8 Significant ^{1}H and ^{13}C NMR chemical shifts of **4-90** and 12-*epi*-**4-90**



4-90 12-*epi*-**4-90**

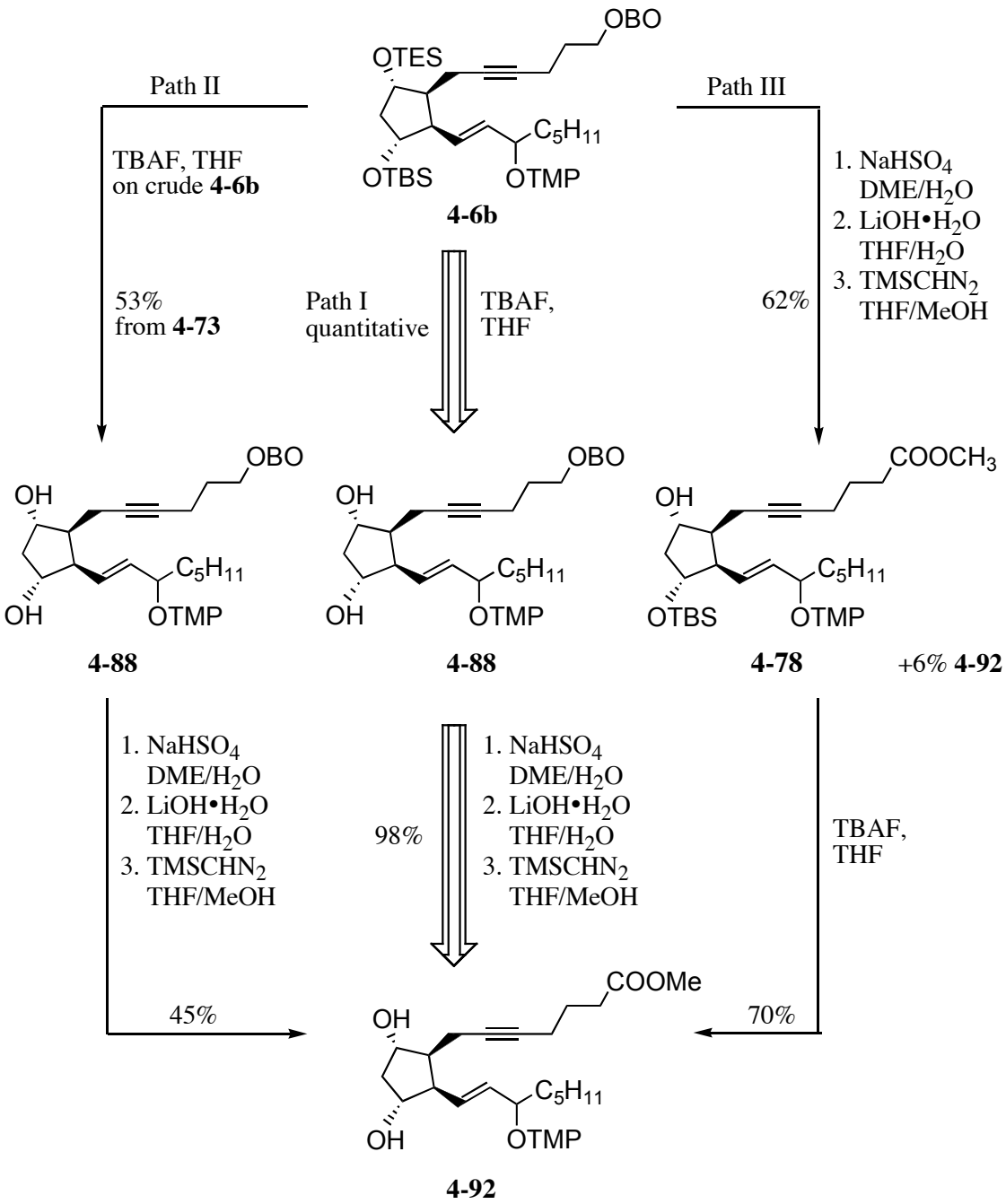
Further characteristic NMR resonances of compounds **4-90**, 12-*epi*-**4-90**, **4-89**, 12-*epi*-**4-89** and **4-91** are presented in Table 6.8.

4.8.3. Synthesis of methyl ester 4-92 from alkylation product 4-6b

Synthetic approaches to methyl ester **4-92** starting from the alkylation product **4-6b** are presented in Scheme 4.35.

Path I. Diol **4-88** (15α/β 1:1) was synthesised quantitatively from **4-6b** by treating pure **4-6b** (15α/β 1.2:1) with TBAF. To synthesise the acid, compound **4-88** was treated with $NaHSO_4$, followed by immediate saponification. The NMR spectrum of the crude acid was showing broad signals and its solubility in ethyl acetate was very low. The crude acid was therefore immediately esterified in the same flask.

Scheme 4.35 Synthesis of methyl ester **4-92**



Methyl ester **4-92** (15α/β 1:1) was obtained in 98% yield from **4-88**. The stereochemistry of the 15-position in **4-92** could however not be determined.

Path II. Deprotection of the silyl groups in crude **4-6b** with TBAF afforded diol **4-88** (15α/β 1:1) in 53% yield from the triflate **4-73** (15α/β 1:1.2). Treatment of **4-88** with aqueous $NaHSO_4$ solution, followed by saponification with LiOH and finally esterification with trimethylsilyldiazomethane provided the methyl ester **4-92** in 45% yield from **4-88**.[152] The isomer ratio was 1.2:1.

Path III. The transformation of OBO-ester **4-6b** (15α/β 1.2:1) to methyl ester **4-78** (15α/β 1:1) was performed before deprotection of the silyl groups. Methyl ester **4-78** was synthesised similarly from **4-6b** in 62% yield, accompanied by 6% of **4-92.** The conditions were mild enough for survival of TES-group until the acidic workup after esterification. The advantage of this approach is that the methyl ester **4-78** as well as its carboxylic acid precursor are much better soluble in organic solvents than **4-92** and its acid precursor, therefore this alternative was easier to monitor by NMR spectroscopy. The yield loss (total yield only 43% of **4-92** from **4-6b**) may be due to partial deprotection of the silyl groups during the sequence. Methyl ester **4-92** (15α/β 1:1) was isolated in 70% after deprotection of the TBS-group with TBAF.

Table 4.25 Significant NMR data of compounds **4-88**, **4-78** and **4-92**

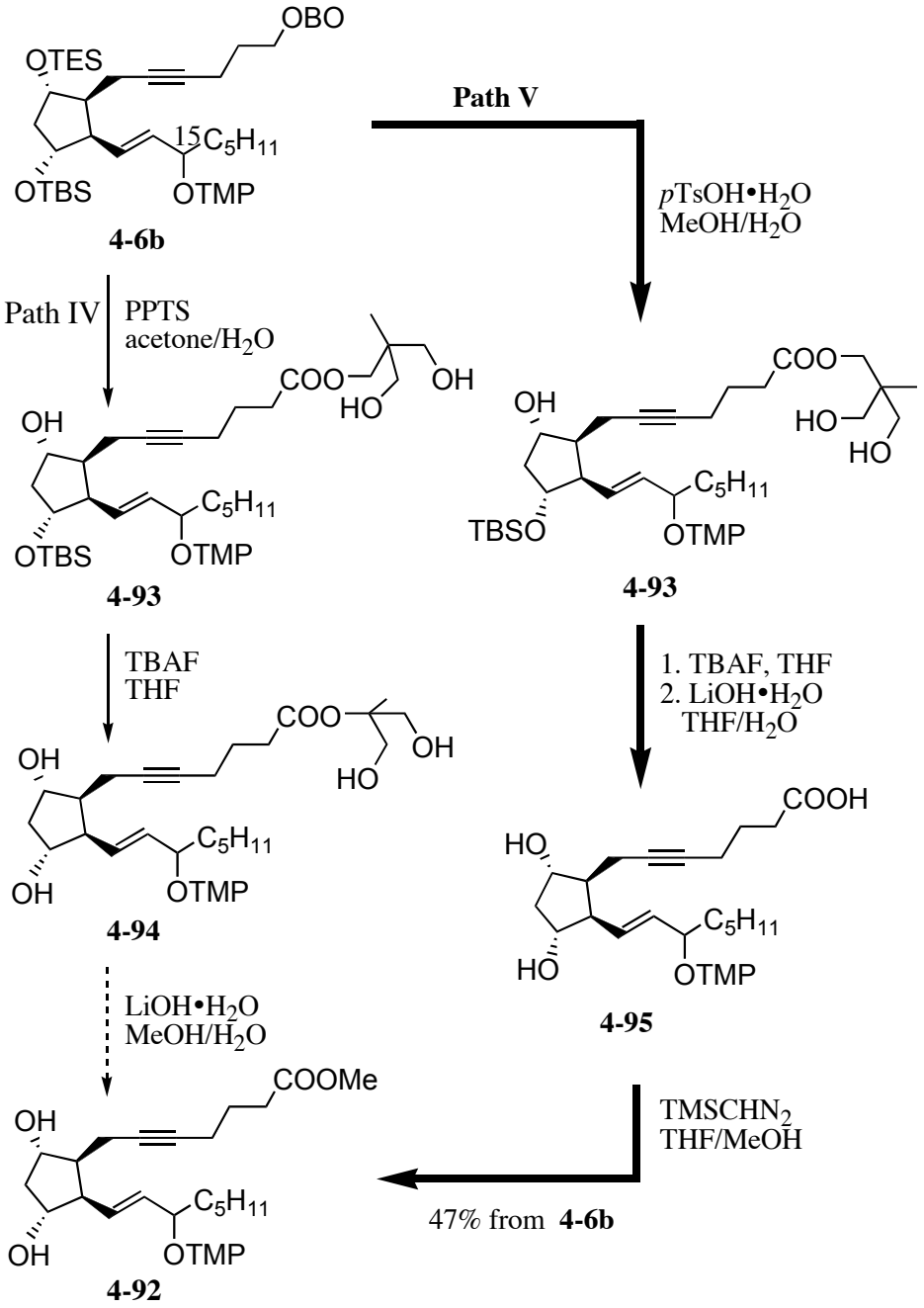
Product	H8	H9	H11	H12	H13	H14	H15
4-88 I_1	2.42 (m)	4.08 (dt)	4.00 (dd)	2.89 (m)	5.31 (dd)	5.57 (dd)	4.22 (m)
4-88 I_2	2.50 (m)	4.18 (dt)	3.96 (ddd)	2.89 (m)	5.28 (dd)	5.60 (dd)	4.22 (m)
4-92 I_1	2.40 (m)	4.07 (dt)	3.85 (dt)	2.78 (m)	5.25 (dd)	5.53 (dd)	4.22 (m)
4-92 I_2	2.34 (m)	3.97 (dt)	3.91 (m)	2.78 (m)	5.24 (dd)	5.56 (dd)	4.22 (m)
4-78 I_1	2.39 (m)	4.00 (m)	3.92 (dt)	2.89 (m)	5.22 (dd)	5.48 (dd)	4.17 (m)
4-78 I_2	2.37-2.47 (m)	3.85 (m)	4.00 (m)	2.89 (m)	5.06 (dd)	5.49 (dd)	4.12 (dt)
	C8	C9	C11	C12	C13	C14	C15
4-88 I_1	50.4 (d)	76.28 (d)	76.0 (d)	54.5 (d)	130.4 (d)	136.3 (d)	85.8 (d)
4-88 I_2	50.8 (d)	76.34 (d)	76.41 (d)	53.9 (d)	130.9 (d)	135.9 (d)	85.3 (d)
4-92 I_1	50.4 (d)	76.4 (d)	76.3 (d)	53.9 (d)	130.6 (d)	136.1 (d)	85.3 (d)
4-92 I_2	50.1 (d)	76.3 (d)	75.9 (d)	54.4 (d)	130.1 (d)	136.5 (d)	85.6 (d)
4-78 I_1	50.2 (d)	76.5 (d)	77.3 (d)	54.4 (d)	129.4 (d)	136.1 (d)	85.2 (d)
4-78 I_2	50.3 (d)	76.7 (d)	77.2 (d)	55.0 (d)	128.7 (d)	136.6 (d)	85.7 (d)

The characteristic chemical shifts of the 15α,β-**4-88** isomers resembled those of their precursors **4-6b**. The silyl group resonances disappeared, however, from the ^1H and ^{13}C NMR

spectra. Similar trends of the NMR data were observed for derivatives **4-78** and **4-92** (Table 4.25). The methyl ester function in compounds 15α,β-**4-78** and 15α,β-**4-92** gave in the ^{1}H NMR spectra singlets at 3.31, 3.32 ppm and at 3.23, 3.24 ppm, respectively. In ^{13}C NMR spectra the methyl ester was characterised by a quartet at 51.0-51.1 ppm for the methyl and a singlet at 172.9-173.1 ppm for the carbonyl group.

Further attempts to optimise the synthesis of methyl ester **4-92** from the alkylation product **4-6b** are presented in Scheme 4.36.

Scheme 4.36 Further attempts to synthesise methyl ester **4-92**



Path IV. The orthoester group in compound **4-6b** (15α/β approx. 1:1.3) was hydrolysed with PPTS in acetone/water.[153] The NMR spectra revealed that the TES-group was simultaneous deprotected while the signals of the TBS-group were still present. The crude compound **4-93** was treated with TBAF to remove the TBS-groups. The resulting tetraol **4-94** was subjected to LiOH in MeOH/water to affect transesterification to **4-92**.[153] A mixture containing **4-92** and free acid **4-95** was obtained, which could not be well separated. Therefore this path was not pursued further. It was thus necessary to conduct saponification and esterification in separate steps.

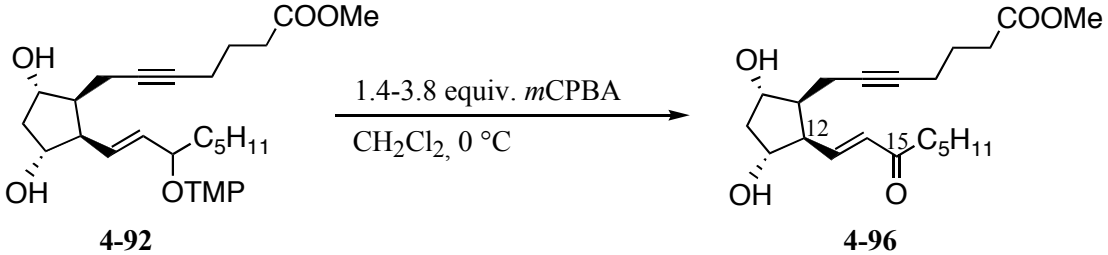
Path V. Treatment of **4-6b** (15α/β approx. 1:1.3) with *p*TsOH in MeOH/water afforded crude diol ester **4-93**. The remaining silyl groups in **4-93** were deprotected with TBAF. Treatment with LiOH in THF/water furnished the free acid **4-95**. Esterification of the latter was carried out with trimethylsilyldiazomethane in THF/MeOH. Methyl ester **4-92** was obtained in 47% yield over 4 steps from **4-6b** (d.r. in 15-position 1.3:1).

Key results: The synthesis of methyl ester **4-92** from OBO-ester **4-6b** was best accomplished via path I (in Scheme 4.35) in excellent yields. Path III was also a productive alternative, and also easier to monitor.

4.8.4. Oxidative deprotection of the TMP functionality in 15-position of 4-92

The synthesis of 15-enone **4-96** was achieved by oxidative deprotection of the 2,2,6,6-tetramethylpiperidinyloxy unit in methyl ester **4-92** employing *m*CPBA (Scheme 4.37, Table 4.26). When compound **4-92** was treated with excess of *m*CPBA at 0 °C for 30 min, ketone **4-96** was obtained in 53% yield as a pure diastereomer (entry 1). Epimerisation in 12-position occurred during storage giving **4-96** and its 12-epimer in a ratio of >10:1.

Scheme 4.37 Oxidative removal of the TMP-functionality in ester **4-92**



4-92 **4-96**

Table 4.26 Optimisation of the oxidative deprotection of the TMP unit

Entry	Conditions	Yield (%)
1	3.8 equiv. *m*CPBA, 30 min	53 (**4-96**:12-*epi*-**4-96** >10:1)
2	1.4 equiv. *m*CPBA, 10 min	93
3	2 equiv. *m*CPBA, 8 min	73

The treatment of **4-92** with 1.4 equivalents of *m*CPBA at 0 °C for 10 min furnished **4-96** in 93% yield as a single diastereomer, as evidenced by the 200 MHz NMR spectrum (entry 2). To avoid epimerisation **4-96** was reduced immediately. Similar results were obtained with 2 equivalents of *m*CPBA (entry 3).

The disappearance of the resonances of the CH group in 15-position (4.22 ppm in the ^{1}H NMR spectrum, and the doublets at 85.3 and 85.6 ppm in the ^{13}C NMR spectrum), and the 2,2,6,6-tetramethylpiperidinyl resonances indicated the formation of **4-96**. The proton and carbon atoms of the double bond shifted downfield at 13-position from 5.24/5.25 ppm and 130.6/130.1 ppm to 6.64 ppm and 143.4 ppm, respectively. The proton in 14-position similarly shifted from 5.53/5.56 to 6.10 ppm. The doublet of doublets with 15.6 and 0.7 Hz coupling constants evidenced that the hydrogen atom in 14-position has only the hydrogen atom in the 13-position as a neighbour. NOESY experiments confirmed the relative isoprostane configuration at the ring.

4.8.5. Reduction of the ketone 4-96 in 15-position

Reductions of the ketone in 15-position were performed previously either racemic with $NaBH_4$ or enantioselectively.[86] Until now no diastereoselective reduction of the carbonyl group in 15-position in a racemic isoprostane was reported.

Yamamoto used a diastereoselective reduction in a racemic synthesis of prostaglandin $F_{2\alpha}$.[154] The reagent diisobutylaluminum 2,6-di-*tert*-butyl-4-methyl phenoxide **4-97** was generated in situ from 2,5-di-*tert*-butyl-4-methylphenol and DIBAL-H. This method was adapted for the reduction of **4-96** (Scheme 4.38, Table 4.28).

At 0.08*M* reagent concentration the conversion reached 50% during a reaction time of 3 h. Triolesters 15α- and 15β-**4-98** were isolated with a ratio of 1.4:1 (entry 1). By applying Yamamoto's original conditions (0.2*M* reagent solution), the 15α:15β diastereomeric ratio improved to 1.7:1, while the yield increased to 92% (entry 2). When the temperature was raised slower over a prolonged reaction time of totally 9 h, **4-98** was obtained in 92% with

15α:β 1.8:1 (entry 3). The two diastereomers 15α-**4-98** and 15β-**4-98** were separated by flash chromatography.

Scheme 4.38 Reduction of ketone **4-96**

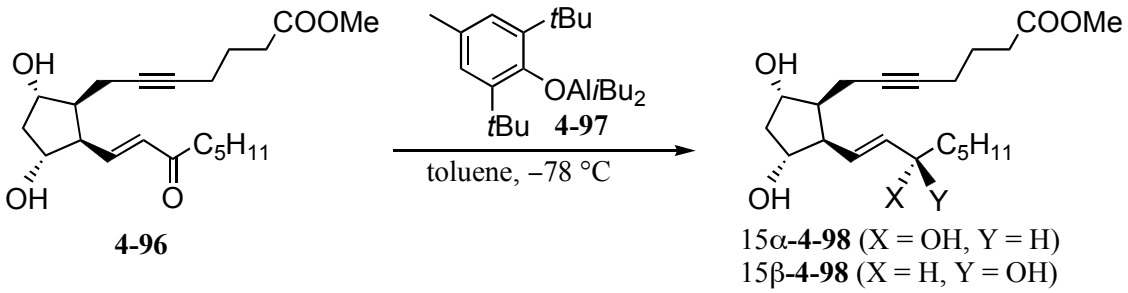


Table 4.28 Optimisation of the reduction conditions

Entry	**4-97** (equiv./conc.)	Conditions	**4-98** (%, 15α:15β)
1	10/0.08*M*	–80 - –40 °C/3 h	50 (1.4:1)
2	12/0.20*M*	–95 - –40 °C/5 h, then –50 - –10 °C/80 min	92 (1.7:1)
3	10/0.20*M*	–80 °C/3 h, –80 - –50 °C/1 h, –50 °C/2.5 h, –50 - –15 °C 2.5 h	92 (1.8:1)

The assignment of the ring configuration was established by NOESY experiments. The proton in 15-position gave a quartet at 4.06 ppm in 15α-**4-98** and at 4.08 ppm in 15β-**4-98**, respectively. The OH-bearing carbon at the same position gave a doublet at 72.6 and 72.9 ppm, respectively, in the ^{13}C NMR spectrum. The configuration of the alcohol in 15-position was assigned by comparison with the data reported by Durand, who have synthesised the same compounds enantiomerically pure.[124c] The more polar diastereomer was 15α-**4-98**. Other significant NMR data are presented in Table 4.28.

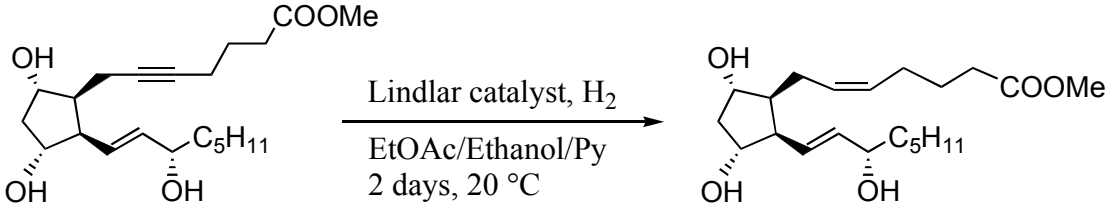
Table 4.28 Chemical shifts and multiplicities of compounds 15α-**4-98** and 15β-**4-98**

Substrate	H8	H9	H11	H12	H13	H14	H15
15α-**4-98**	2.32 (m)	4.14 (dt)	4.03 (q)	2.78 (dt)	5.42 (dd)	5.59 (dd)	4.06 (q)
15β-**4-98**	2.34 (m)	4.15 (dt)	4.03 (dd)	2.80 (dt)	5.44 (dd)	5.62 (dd)	4.08 (q)
Substrate	C8	C9	C11	C12	C13	C14	C15
15α-**4-98**	49.69 (d)	76.23 (d)	76.08 (d)	53.4 (d)	128.3 (d)	136.62 (d)	72.61 (d)
15β-**4-98**	49.71 (d)	76.21 (d)	76.06 (d)	53.6 (d)	127.7 (d)	136.7 (d)	72.9 (d)

4.8.6. Hydrogenation of the alkyne

The hydrogenation of the alkyne group in compound **4-98** to the 5,6-(*Z*)-double bond was explored with two catalysts (Scheme 4.39, Table 4.29). Employment of P-2 Ni[124c] as the catalyst was not effective with **4-98**, which was recovered unchanged (entry 1). Lindlar's catalyst exhibited under classical conditions (in ethyl acetate, in the presence of pyridine) also no activity with this substrate (entry 2). The employment of ethanol as cosolvent made the difference. Performing the hydrogenation reaction with the pure alkyne 15α-**4-98** in a mixture of ethyl acetate/ethanol gave the methyl ester of 15α-F_{2t}-IsoP 15α-**4-1** in 96% yield. Similarly, 15β-**4-98** provided the methyl ester of 15β-F_{2t}-IsoP 15β-**4-1** in 99% yield under the same conditions.

Scheme 4.39 Selective hydrogenation of the alkyne unit in **4-98**



4-98 15α-**4-1** (15α-F_{2t}-Isoprostane)

Table 4.29 Optimisation of hydrogenation conditions

Entry	Condition	Yield
1	$Ni(OAc)_2$, $NaBH_4$, $(CH_2NH_2)_2$, H_2, Ethanol, 20 °C	No reaction
2	Lindlar's Catalyst, EtOAc/Py	No reaction
3	Lindlar's Catalyst, EtOAc/EtOH/Py 2:1:0.2	15α-**4-1** 15-F_{2t}-IsoP 96%
4	Lindlar's Catalyst, EtOAc/EtOH/Py 2:1:0.2	15β-**4-1** 15-F_{2t}-IsoP 99%

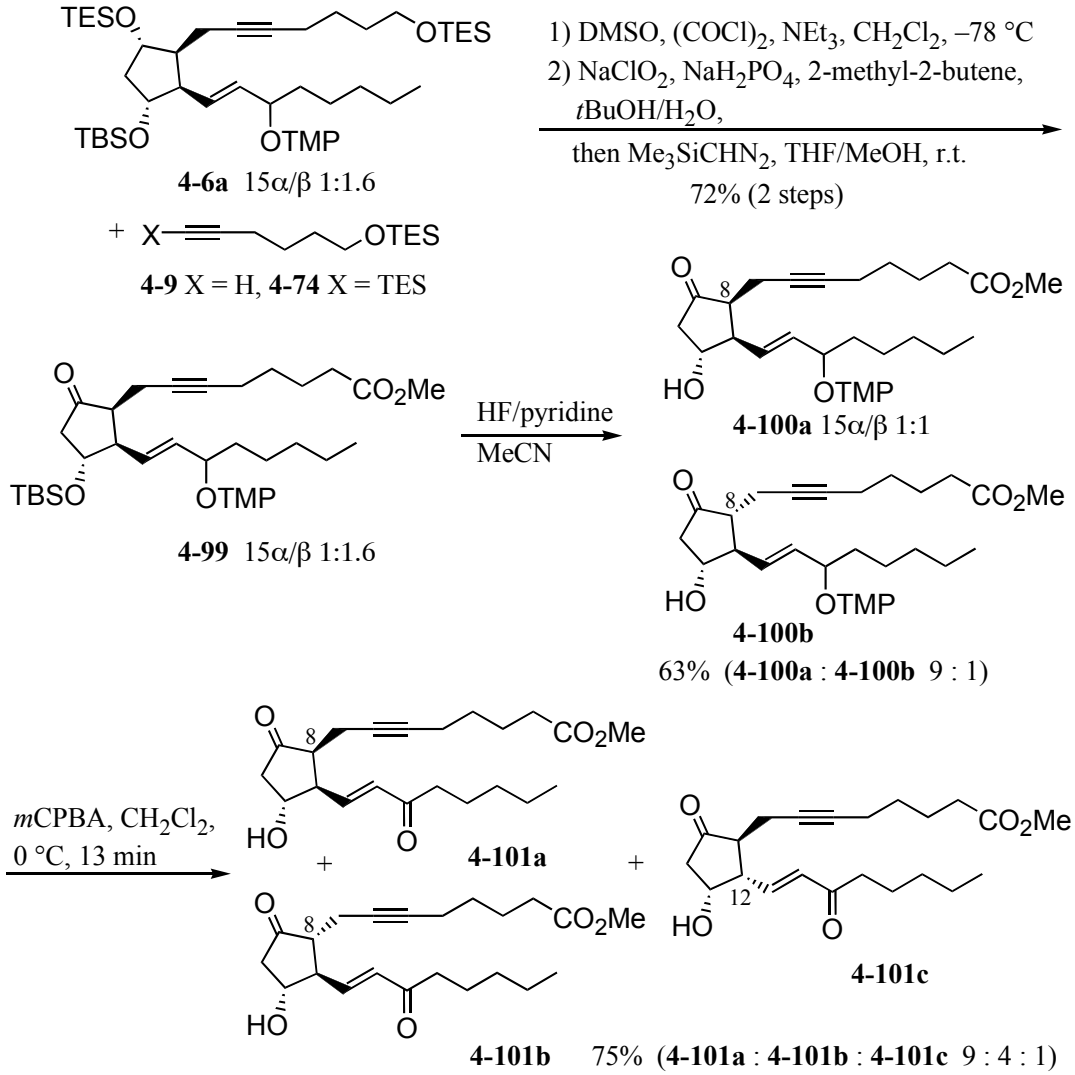
The characteristic alkyne resonances were absent in the ^{13}C NMR spectra of products 15α-**4-1** and 15β-**4-1**. Instead, four doublets in the range 128.4-136.3 ppm pointed to the presence of two double bonds. This was supported by signals in the ^{1}H NMR at 5.43-5.45 ppm (three protons) and at 5.59-5.60 ppm (one proton). Further NMR data are presented in Table 4.30. The relative ring configuration in 15α-**4-1** and 15β-**4-1** was established by comparison to the substrates 15α-**4-98** and 15β-**4-98**. For 15α-**4-1** it was additionally confirmed via NOESY experiments.

Table 4.30 Chemical shifts and multiplicities of 15-F_{2t}-IsoP 15α-**4-1** and 15β-**4-1**

Compound	H8	H9	H11	H12	H13	H14	H15
15α-**4-1**	2.18 (m)	3.98 (dt)	4.05 (dt)	2.78 (dt)	5.43 (m)	5.59 (dd)	4.08 (q)
15β-**4-1**	2.20 (m)	4.00 (m)	4.04 (ddd)	2.79 (ddd)	5.45 (m)	5.60 (dd)	4.09 (q)
Compound	C8	C9	C11	C12	C13	C14	C15
15α-**4-1**	50.80 (d)	74.46 (d), 76.47 (d)		53.66 (d)	128.81	136.20	72.78 (d)
15β-**4-1**	50.72 (d)	76.54 (d), 76.62 (d)		53.71 (d)	128.43 (d)	136.29 (d)	72.70 (d)

4.9. The first total synthesis of 13,14-dihydro-15-oxo-15-E_2-isoprostane methyl ester 4-3 and of 13,14-dihydro-15-oxoprostaglandin E_2 methyl ester 4-4

Scheme 4.40 Synthesis of enones **4-100a,b**

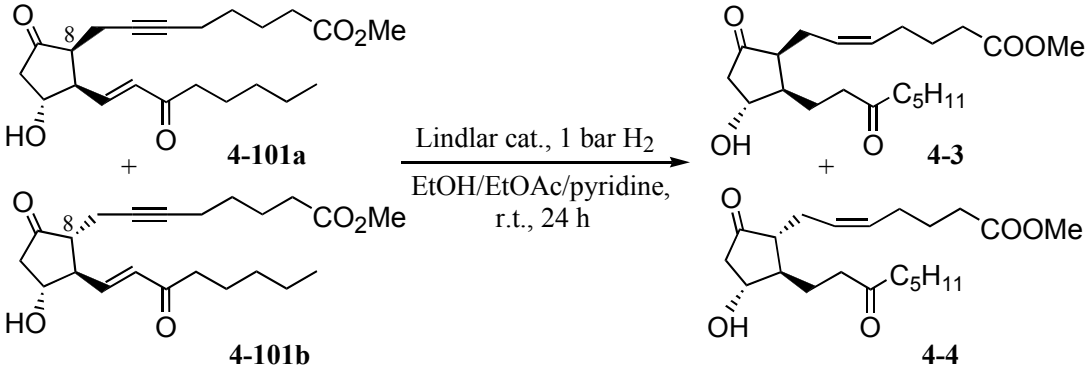


Compound **4-6a** served as the starting material (Scheme 4.40). The triethylsilyloxy functionalities were oxidised under Swern conditions.[155, 156] The resulting crude keto aldehyde

was oxidised further to the acid,[157] which was immediately esterified with trimethylsilyldiazomethane providing methyl ester **4-99** in 72% yield. The TBS-ether in the 11-position of **4-99** was deprotected with pyridine-HF in CH_3CN, affording compounds 15α,β-**4-100a** in 63% yield and a 1:1 ratio. The stereochemistry in 15-position could not be assigned. Some epimerisation of 8-position occurred under these conditions giving a 9:1 mixture of **4-100a**/**4-100b**. Compound **4-100b** was found as a single diastereomer, however its configuration at 15-position could not be elucidated. The alkoxyamine in **4-100a** and **4-100b** was oxidatively removed with *m*CPBA in CH_2Cl_2.[151] Extensive epimerisation occurred in 8-position,[158] affording an inseparable mixture of **4-101a** and **4-101b** 2.25:1 in 75% yield. Small amounts of **4-101c** were detected, revealing some epimerisation in 12-position as well.

The mixture of **4-101a**, **4-101b** and **4-101c** was subjected to Lindlar hydrogenation (Scheme 4.41). Under the conditions developed for alkyne reduction in the synthesis of F_{2t}-IsoP, the alkyne and the enone were reduced successfully. A partially separable mixture of diastereomers **4-3** and **4-4** was obtained in excellent yields in a ratio of 1.5:1. Hence, under the slightly basic conditions further epimerisation at the 8-position occurred. The structure of **4-3** was established by means of its NMR data. The structure and configuration of PGE_2 derivative **4-4** was assigned by comparison of its NMR data with those of authentic 13,14-dihydro-15-oxo-PGE_2 methyl ester, which was synthesised by esterification of commercially available 13,14-dihydro-15-oxo-PGE_2.[159]

Scheme 4.41 Lindlar hydrogenation of **4-101a,b,c**



4-101a:**b**:**c** 9 : 4 : 1

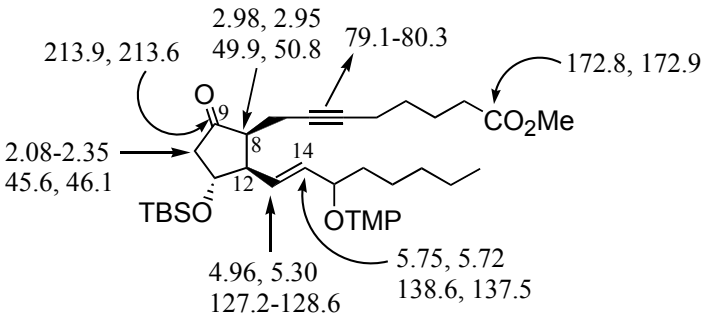
90% (**4-3** : **4-4** 1.5 : 1)

The structure assignment of compounds **4-99**, **4-100a,b**, **4-101a,b,c**, **4-3** and **4-4** was performed based on NMR experiments.

The NMR spectra confirmed the successful transformation of **4-6a** to **4-99** (Figure 4.9). The silyloxy group in 9-position disappeared. Instead the carbonyl group at 9-position appeared as a singlet at 213.9 and at 216.6 ppm, respectively, for isomers 15α,β-**4-99**. The

methyl ester protons gave a singlet at 3.33 ppm in the ^{1}H NMR spectrum for both 15α-**4-99** and 15β-**4-99.** The ester carbon was a singlet at 172.9 and 172.8 ppm, respectively.

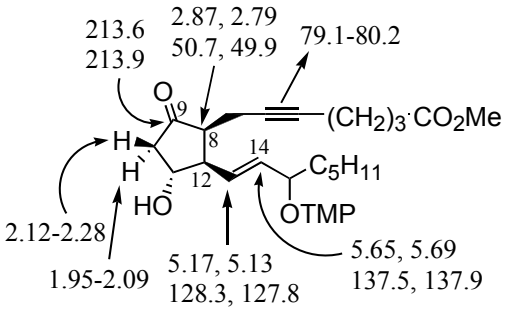
Figure 4.9 Significant chemical shifts of derivatives 15α-**4-99** and 15β-**4-99**.



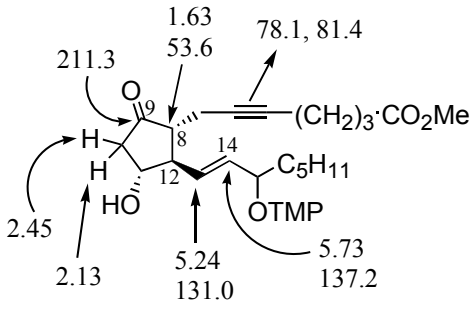
15α-**4-99** and 15β-**4-99**

The *t*-butyldimethylsilyloxy group in 11-position disappeared in isomers 15α,β-**4-100a** and **4-100b**. In IsoP-isomers 15α,β-**4-100a** protons at the 8-position absorbed at 2.79-2.87 ppm (Figure 4.10). The carbon atoms of the same position gave a doublet at 49.9 ppm and 50.7 ppm, respectively. In contrast the proton at the 8-position of PG-isomer **4-100b** was upfield-shifted by 1.16 ppm absorbing at 1.63 ppm. The carbon atom at this position was slightly downfield shifted absorbing at 53.6 ppm. Another distinguishing difference between IsoP and PG-isomers was the difference of the C13 and C14 chemical shifts. For 15α-**4-100a** and 15β-**4-100b** this difference amounts 9.2 ppm and 10.1 ppm, respectively. For **4-100b** it was much smaller with a value of 6.2 ppm. Further significant NMR data of these compounds are presented in Figure 4.10 and Table 6.9.

Figure 4.10 Significant ^{1}H and ^{13}C NMR data of compounds **4-100a** and **4-100b**



15α-**100a** and 15β-**100a**

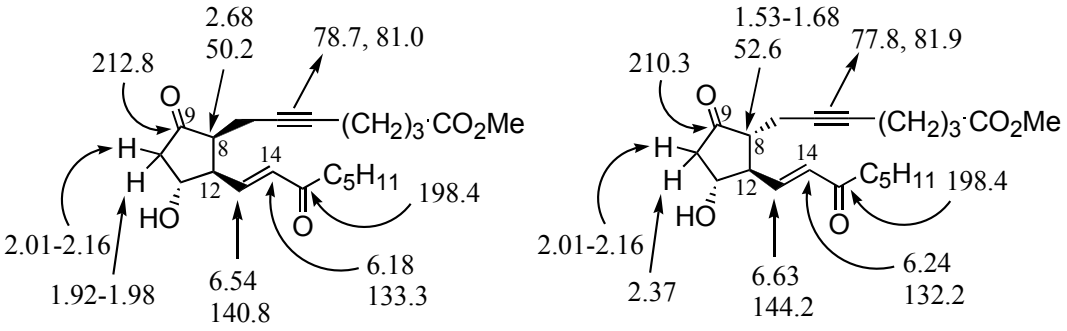


4-100b

The carbonyl group in 15-position of **4-101a** and **4-101b** absorbed at 198.4 ppm (Figure 4.11). The enone proton at 13-position of **4-101a** and **4-101b** was more downfield-shifted than in substrates **4-100a,b**, giving a doublet of doublets at 6.54 and 6.63 ppm, respectively. A similar downfield shift was observed for the protons in 14-position. The

carbon atoms in 13-position were also downfield-shifted at 140.8 ppm for **4-101a** and at 144.2 ppm for **4-101b**. Further significant NMR data are presented in Figure 4.11 and Table 6.9.

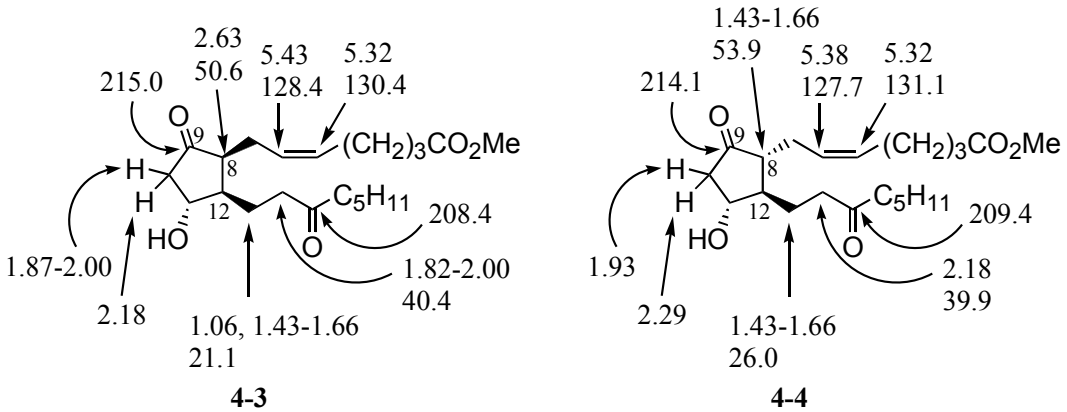
Figure 4.11 Significant NMR data of compounds **4-101a** and **4-101b**



4-101a **4-101b**

The structure of 13,14-dihydro-15-oxo-15-E_2-IsoP **4-3** and of **4-4** was elucidated by means of their NMR data (Figure 4.12). The connectivity was established by COSY and HSQC experiments. The enone resonances disappeared in the NMR spectra. In compound **4-3** the protons and carbon atoms of the 13- and 14-positions absorbed in the alkyl range. The protons of the new C5-C6 double bond absorbed at 5.43 and 5.32 ppm, while the carbon atoms appeared as a doublet at 128.4 and 130.4 ppm, respectively. Similar resonances were observed for **4-4**. Its structure was additionally confirmed by comparison with the methyl ester synthesised from commercially available 13,14-dihydro-15-oxo-PGE_2. The most significant difference between **4-3** and **4-4** was the chemical shift of H8.

Figure 4.12 Significant NMR data of compounds **4-3** and **4-4**



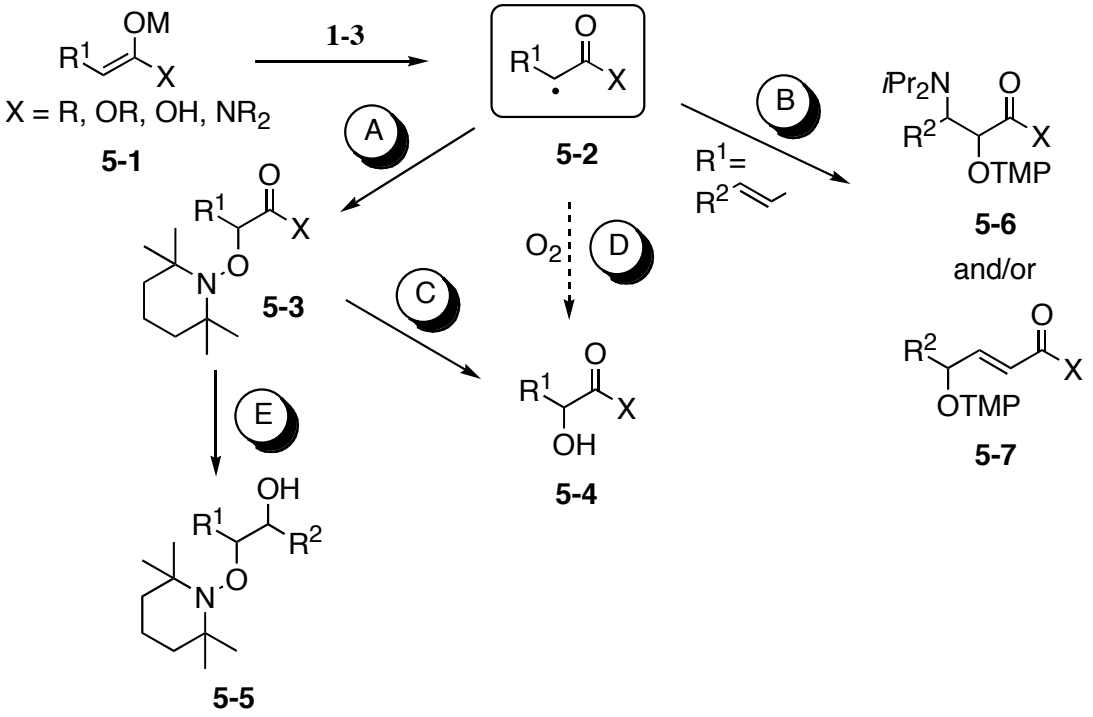
4-3 **4-4**

Key results: The first synthesis of the potential 15-E_2-IsoP metabolite **4-3** and of racemic 13,14-dihydro-15-oxo-PGE_2 **4-4** was accomplished in 11 steps and 1.4% overall yield. The availability of synthetic material facilitates the study of 15-E_2-IsoP metabolism.

5. Conclusions and outlook

With this work significant contributions concerning oxidative reactions of enolates were achieved. Based on the convenient generation of α-carbonyl radicals **5-2** from **5-1** by outer sphere single electron transfer with ferrocenium hexafluorophosphate, new methodologies were developed: 1) Radical α-functionalisation; 2) Radical dimerisations and 3) Selective radical cyclisations and their application to the total synthesis of natural products.

Scheme 5.1 α-Oxygenation of carbonyl compounds

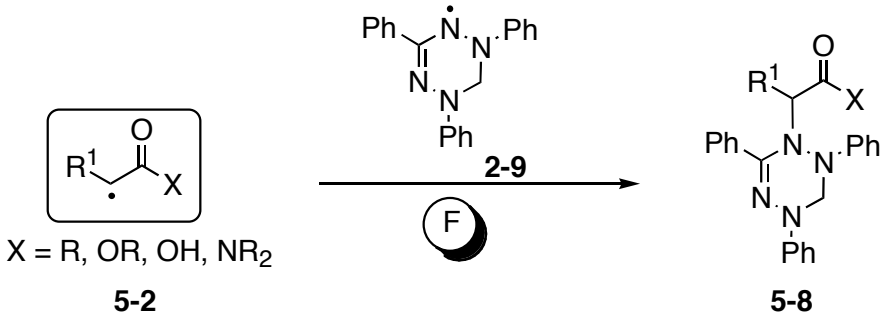


1) An efficient *α-oxygenation* method for the synthesis of carbonyl compounds of type **5-3** was established (Scheme 5.1, Path A). The scope covers most classes of carbonyl compounds and nitriles. This method, adapted for unsaturated carbonyl compounds, gave access to products of type **5-6** and **5-7** in low yield (Path B). Amide conjugate addition/oxygenation prevailed. The chemoselectivity was partially controlled by using HMPA as cosolvent.

Compounds **5-3** are valuable building blocks, which were successfully transformed to α-hydroxy carbonyl compounds **5-4** by reductive deprotection of the tetramethylpiperidinyl group (Path C). The direct oxidation of the enolate **5-1** with oxygen gave only small amounts of product **5-4** and could not be further developed to a reliable method (Path D). Chemoselective reduction of the carbonyl group allows the efficient synthesis of TMP-monoprotected diols **5-5**.

A new radical *α-amination* of carbonyl compounds by oxidative coupling of their enolates with the persistent verdazyl radical **2-9** was developed (Scheme 5.2).

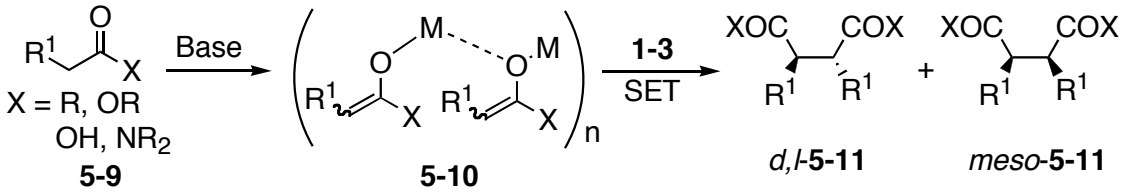
Scheme 5.2 α-Amination of carbonyl compounds



Compounds of type **5-8** can be synthesised from esters in high yields. However the same conditions applied to 3-oxo esters and nitriles gave rearrangement reactions forming new triazoles and tetrazoles. The radical *α-amination* needs on one hand further investigations to establish the scope. On the other hand a detailed mechanistic study of the rearrangement reactions is necessary.

2) The oxidative coupling of enolates induced by the outer sphere oxidant ferrocenium hexafluorophosphate was established for the synthesis of 1,4-dicarbonyl compounds ***d,l*-5-11** and ***meso*-5-11** from ketones, esters, acids and amides (Scheme 5.3). While ketones and esters react efficiently, the formation of dimers derived from acids and amides is accompanied by competing disproportionation reactions. However the method does not work for selected lactones or nitriles.

Scheme 5.3 Oxidative coupling of enolates



A large body of knowledge was accumulated on the mechanism of radical dimerisations. Aggregation of enolates in superstructures like **5-10**, conservation of enolate geometry in the α-carbonyl radical, the mechanism of the electron transfer (inner or outer

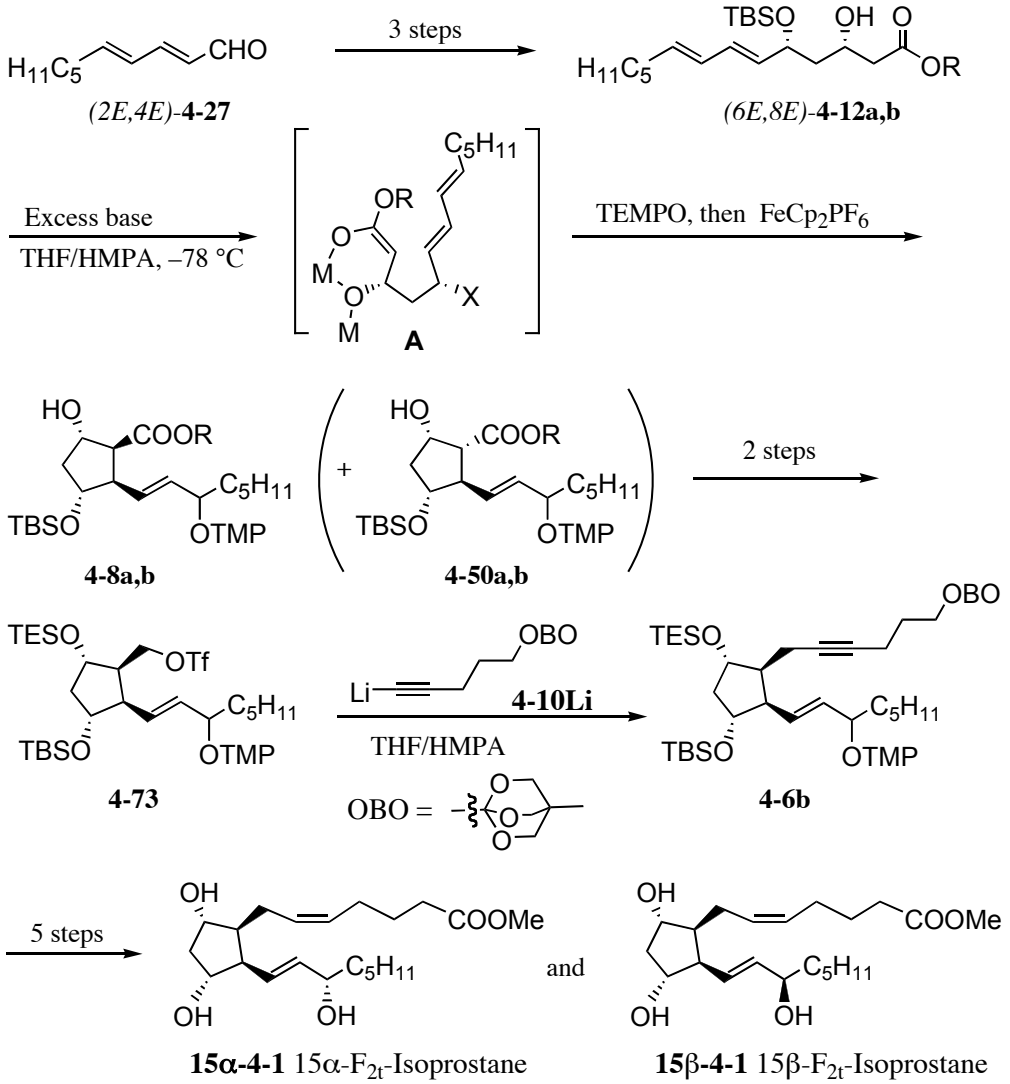
sphere), and the presence of additives significantly influenced the yields and the diastereoselectivity of the dimerisation.

Exceptionally high diastereoselectivity was achieved in the dimerisations of aromatic ketones. Esters, acids and amides dimerised with low to moderate diastereoselectivities.

Oxidative dimerisations should be further studied especially for improving diastereoselectivity. Chiral or achiral ligands at the metal counterion, or a different generation of the enolate may be promising in this sense.

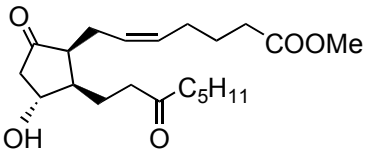
3) A conceptually new synthesis of the methyl ester of F_{2t}-isoprostane **15α-4-1** and its 15-epimer **15β-4-1** was achieved in 12 steps and 14% overall yield, which makes it one of the most efficient of the existing syntheses (Scheme 5.4).

Scheme 5.4 Schematic representation of the total synthesis of 15α- and 15β-F_{2t}-IsoP **4-1**

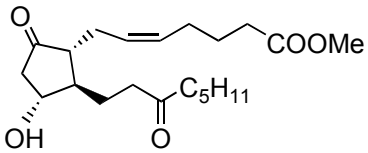


- The assembly of the C7-C20 chain *(6E,8E)*-**4-12a,b** was achieved via a short 3 step synthesis, consisting of a vinylogous aldol addition, a *syn*-selective reduction of a 5-hydroxy keto ester and a highly regioselective silylation of the resulting diol.
- A new oxidative radical anion cyclisation/oxygenation methodology gave access to the preparation of both IsoP- and PG-skeletons **4-8a,b** and **4-50a,b** from the same substrate, as well as the introduction of the oxygen source, the TMPO-group, in the 15-position. The developed cyclisation model proved to be generally applicable for similar precursors, and facilitated the stereodivergent synthesis of the central cyclopentane systems of F_{2t}-IsoP, A_2-IsoP, PG $F_{2\alpha}$, PG A_2 and E_2-IsoP. This was achieved by controlled manipulation of the chelating properties of different metal counterions of the enolate anion **A**, as well as the oxidatively generated radical anion intermediates.
- The introduction of the C1-C7 chain was accomplished by linking C6 and C7 via an alkylation with an alkynyllithium. This completion of C20 skeleton **4-6b** is completely new in the synthesis of isoprostanes, and was only rarely used in the synthesis of prostaglandins.
- The total synthesis is an archetype for the preparation of other isoprostanes, many of which could not be studied simply because of material deficiency.
- The approach was adapted to the first synthesis of potential central metabolites of 15-E_2-isoprostane **4-3** and **4-4** (Figure 5.1). The completion of the C20 skeleton was conducted similarly to the F_{2t}-IsoP synthesis. Further steps of the total synthesis were particularly adapted for the preparation of E_2-IsoP metabolites, which was accomplished in 11 steps and an overall 1.4% yield. The access facilitates the in vivo study of E_2-IsoP metabolism, as well as production of enough material, to investigate its biological activities. The high epimerisation sensitivity of the 9-position suggests that autoxidatively formed E_2-IsoP exhibits to some extent a common pathway with the metabolism of PGE_2.

Figure 5.1 Structures of **4-3** and **4-4**



13,14-Dihydro-15-oxo-E_2-IsoP **4-3**



13,14-Dihydro-15-oxo-PGE_2 **4-4**

- This methodology was also applied to the synthesis of the complete C20 skeleton of A_2-isoprostane and can be applied to the synthesis of other, less studied oxidative stress metabolites in humans or plants like neuroprostanes or phytoprostanes.

6. Experimental Part

General: All reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen. THF, CH_2Cl_2, MeOH, toluene, NEt_3, 2,6-lutidine, HMPA, pyridine and ferrocenium hexafluorophosphate were dried following standard methods under nitrogen atmosphere. TLC plates POLYGRAM SIL G/UV_{254} (Macherey-Nagel) were used for monitoring reactions. Flash column chromatographic separations were performed on silica gel 60 (Fluka, 230-400 mesh). IR spectra were taken on a Bruker Tensor 27 spectrometer (Dura Sample Diamant-ATR, 1 Reflexion). ^{1}H and ^{13}C NMR spectra were recorded, unless otherwise noted, in $CDCl_3$ on Bruker AV II 600, DRX 400, AV 300 or AC 200 spectrometers at 600, 400, 300 or 200 MHz for ^{1}H NMR, and 150, 100, 75 or 50 MHz for ^{13}C NMR, respectively. Chemical shifts are provided in ppm vs. TMS as the internal standard. Connectivity was determined by ^{1}H-^{1}H COSY experiments. Stereochemical assignments are based on NOE-Diff and NOESY experiments. ^{13}C NMR assignments were obtained from DEPT and HSQC experiments. X-Ray crystallographic analyses were performed on a Bruker SMART 1000 CCD diffractometer using Mo Kα radiation. EI-mass spectra were recorded on Finnigan MAT 95 spectrometers at 70 eV. ESI-mass spectra were obtained on a Finnigan MAT 95XLT or QSTAR Elite system, sample concentration approx. 50 µg/mL in MeOH, spray voltage pos. mode: 1.3 - 1.8 kV, spray voltage neg. mode: 1.1 - 2.3 kV, HRMS resolution: 10000 (10% valley definition), or a Thermo Fisher Scientific LCQ Fleet spectrometer, sample concentration approx. 1 µg/mL. HRMS spectra were measured on a LTQ Orbitrap XL spectrometer, resolution: 100000. Combustion analyses were performed at the Microanalytical Laboratories of the Technical University of Braunschweig.

The syntheses of silyl ketene acetals ***E*-3-75** and ***Z*-3-76** were performed according to the literature.[119] The *E:Z* ratios were in the range 4-7.6:1, and the *Z:E* ratios were in the range 7-8.6:1, respectively.

6.1. α-(2,2,6,6-Tetramethylpiperidin-1-yl-1-oxy) carbonyl compounds 3-2, 3-5 and 3-11 (General procedure):

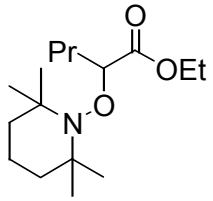
General: *n*BuLi (1.625 mL, 2.6 mmol, 1.6*M* solution in hexane) was added dropwise via syringe to a solution of dry *i*Pr_2NH (0.367 mL, 2.6 mmol) in dry THF (19 mL, 0.1*M*) at –78 °C. After stirring at –78 °C for 0.5 h, the substrate **3-1**, **3-4** or **3-10a-h** (2.0 mmol) dissolved in THF (1 mL) was added dropwise at –78 °C. For compounds **3-1b** and **3-4c,h** the deprotonation was performed with 4-4.6 mmol of LDA (for exact amounts see Tables 3.1 and 3.3). The mixture was stirred at –78 °C for 30 min.

With LiCl: Anhydrous LiCl (399.5 mg or 510 mg, 9.4 mmol or 12 mmol) was flame-dried under high vacuum in a Schenk flask five times for ca. 2 min. Dry THF (19 mL, 0.1*M* solution) followed by dry *i*Pr_2NH (0.367 mL, 2.6 mmol) were added. *n*BuLi (1.625 mL, 2.6 mmol, 1.6*M* solution in hexane) was added dropwise via syringe at –78 °C. After stirring at –78 °C for 0.5 h, the substrate **3-1**, **3-4** or **3-10a-h** (2.0 mmol) dissolved in THF (1 mL) was added dropwise at –78 °C. For compounds **3-1b** and **3-4c,h** the deprotonation was performed with 4-4.6 mmol of LDA (for exact amounts see Tables 3.1 and 3.3). The mixture was stirred at –78 °C for 5-30 min (Tables 3.1-3.3).

With HMPA: *n*BuLi (1.625 mL, 2.6 mmol, 1.6*M* solution in hexane) was added dropwise via syringe to a solution of dry *i*Pr_2NH (0.367 mL, 2.6 mmol) in dry THF (19 mL, 0.1*M*) at –78 °C. After stirring at –78 °C for 0.5 h, the substrate **3-1**, **3-4** or **3-10a-h** (2.0 mmol) dissolved in THF (1 mL) was added dropwise at –78 °C. For compounds **3-1b** and **3-4c,h** the deprotonation was performed with 4-4.6 mmol of LDA (for exact amounts see Tables 3.1 and 3.3). The mixture was stirred at –78 °C for 30 min. Dry HMPA (2.09 mL, 12 mmol) was added via syringe.

TEMPO **1-2** (343 mg, 2.2 mmol) was added in one portion at –78 °C and the mixture was stirred until it dissolved (ca. 5 min). For **3-4h**, 4.2 mmol of TEMPO was used. Ferrocenium hexafluorophosphate **1-3** was added in small portions at –78 °C as it was consumed (the blue colour of the oxidant disappears when added to the enolate solution). Addition was continued until the reaction mixture remained dark blue (0.993 g - 1.32 g, 3.0-3.7 mmol; for **3-4h** a minimum 4 mmol of **1-3** was added). Stirring was continued at –78 °C for 15 min to 1 h and the reaction was monitored by TLC (Ferrocene R_f = 0.9 (hexane/EtOAc, 10:1) and TEMPO R_f = 0.4 (hexane/EtOAc, 10:1)). The reaction was quenched with 3 to 10 drops of water, diluted with 20 mL diethyl ether, warmed to room temperature and filtered through a pad of silica gel, which was washed with diethyl ether. The solvent was evaporated in vacuum, the inhomogeneous mixture was preadsorbed on silica gel, added to a filled column and purified by flash chromatography with hexane/ethyl acetate.

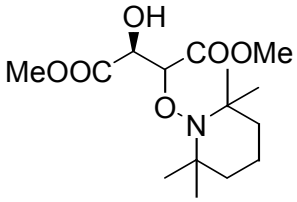
Ethyl 2-(2,2,6,6-tetramethylpiperidin-1-yloxy)pentanoate 3-2a



Flash chromatography (hexane/ethyl acetate 80:1, gradient to 10:1) gave ferrocene, followed by **3-2a** and dimer **3-3a** as pale yellow oils. Yield (7 mmol setup, 6 equiv. LiCl): **3-2a** 1.74 g (87%) and *meso*-**3-3a** 36 mg (4%). Yield (1.5 mmol setup, 6 equiv. HMPA) **3-2a** 275 mg

(64%) and **3-3a** 40 mg (20%, *meso/d,l* 1:1.5). R_f = 0.5 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 0.85 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 0.96 (s, 3H, $NCCH_3$), 1.04 (s, 3H, $NCCH_3$), 1.05 (s, 3H, $NCCH_3$), 1.11 (s, 3H, $NCCH_3$), 1.21 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.14-1.29 (m, 2H, $CH_2CH_2CH_3$), 1.31-1.57 (m, 6H, $NCCH_2CH_2CH_2CN$), 1.73 (m, 2H, $CHCH_2$), 4.09 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.14 (dd, *J* = 7.4, 6.8 Hz, 1H, CHON). - ^{13}C NMR (100 MHz): δ = 14.0 (q, $CH_2CH_2CH_3$), 14.2 (q, OCH_2CH_3), 17.1 (t, $NCCH_2CH_2CH_2CN$), 17.9 (t, $CH_2CH_2CH_3$), 20.0 (q, $NCCH_3$), 20.2 (q, $NCCH_3$), 33.0 (q, $NCCH_3$), 33.5 (q, $NCCH_3$), 34.2 (t, $CH_2CH_2CH_3$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 40.3 (t, $NCCH_2CH_2CH_2CN$), 59.3 (s, $NCCH_3$), 60.1 (t, CH_2O), 85.5 (d, CHON), 173.6 (s, CO_2). - IR (film): $\tilde{\nu}$ = 2964, 2935, 2874, 1748, 1467, 1376, 1362, 1261, 1245, 1181, 1133, 1031 cm^{-1}. - MS (+CI): *m/z* (%) = 286 (100) [M+H$^+$], 164 (12), 142 (22) [TMPH$_2^+$], 126 (13), 116 (12). - Combustion analysis: $C_{16}H_{31}NO_2$ (285.42): calc. C 67.33, H 10.95, N 4.91; found C 67.24, H 11.06, N 5.06.

***syn*- and *anti*-(2*S*)-Dimethyl 2-hydroxy-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)succinates 3-2b**

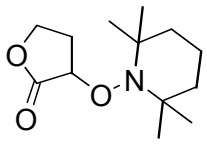


Flash chromatography (hexane/ethyl acetate 20:1, gradient to 1:1) gave ferrocene, followed by *anti*-**3-2b** and a mixture of *syn*- and *anti*-**3-2b** as pale yellow oils. Yield (2 mmol setup, 2.15 equiv. LDA): 410 mg (65%, *syn/anti*-**3-2b** 1:1.8). Yield (2 mmol setup, 2.5 equiv. LDA, deprotonation 1 h at –78 - –50 °C): 600 mg (94%, *syn/anti*-**3-2b** 1:2.2). With 4.7 equiv. LiCl (2 mmol setup, 2.3 equiv. LDA): 410 mg (77%, *syn/anti*-**3-2b** 1:1.4). With 6 equiv. HMPA (2 mmol setup, 2.15 equiv. LDA): 420 mg (66%, *syn/anti*-**3-2b** 1:2). The analyses were performed on a mixture of *syn*- and *anti*-isomers.

IR (film): $\tilde{\nu}$ = 3493 (w), 2933 (w), 1739 (s), 1438 (m), 1363 (w), 1257 (m), 1241 (m), 1200 (s), 1171 (s), 1129 (s), 1080 (s), 1022 (m), 990 (w), 959 (w), 878 (w), 792 (w), 710 (w) cm^{-1}. - MS (ESI) m/z (%): 657 (21) [2M+Na$^+$], 340 (100) [M+Na$^+$], 184 (9) [M–TEMPO+Na$^+$]. - Combustion analysis: $C_{15}H_{27}NO_6$ (317.38): calc. C 56.77, H 8.57, N 4.41; found C 56.98, H 8.71, N 4.22. - Major isomer *(2S,3R)*-**3-2b**: R_f(hexane/EtOAc 2:1) = 0.38. - ^{1}H NMR (200 MHz): δ = 1.15 (br. s, 6H, $NCCH_3$), 1.23 (m, 1H, $NCCH_2CH_2CH_2CN$), 1.25 (s, 6H, $NCCH_3$), 1.48 (br. s, 5H, $NCCH_2CH_2CH_2CN$), 3.32 (br. s, 1H, OH), 3.74 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.81 (s, 2H, CHON, CHOH). - ^{13}C NMR (50 MHz): δ = 16.9 (t, $NCCH_2CH_2CH_2CN$), 20.1 (q, $NCCH_3$), 20.3 (q, $NCCH_3$), 33.0 (q, $NCCH_3$), 33.9 (q, $NCCH_3$), 40.2 (t,

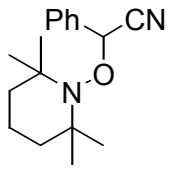
NC*C*H$_2$CH$_2$*C*H$_2$CN), 51.83 (q, O*C*H$_3$), 52.6 (q, O*C*H$_3$), 59.8 (s, N*C*CH$_3$), 60.7 (s, N*C*CH$_3$), 70.9 (d, *C*HOH), 85.8 (d, *C*HON), 169.7 (s, *C*O), 172.3 (s, *C*O). - Minor isomer *(2S,3S)*-**3-2b**: R_f(hexane/EtOAc 2:1) = 0.35. - ^{1}H NMR (200 MHz): δ = 1.04-1.48 (m, 18H, NCCC*H$_2$*C*H$_2$*C*H$_2$*CN, NCC*H$_3$*), 3.74 (s, 3H, OC*H$_3$*), 3.83 (s, 3H, OC*H$_3$*), 4.40 (br. s, O*H*), 4.65 (s, 2H, C*H*ON, C*H*OH). - ^{13}C NMR (50 MHz): δ = 16.8 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.1 (q, NC*C*H$_3$), 20.3 (q, NC*C*H$_3$), 33.0 (q, NC*C*H$_3$), 33.9 (q, NC*C*H$_3$), 40.1 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 51.79 (q, O*C*H$_3$), 52.4 (q, O*C*H$_3$), 59.8 (s, N*C*CH$_3$), 60.7 (s, N*C*CH$_3$), 71.1 (d, *C*HOH), 83.6 (d, *C*HON), 170.2 (s, *C*O), 171.8 (s, *C*O).

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)butyrolactone 3-2c



Flash chromatography (hexane/ethyl acetate 20:1, gradient to 2:1) gave ferrocene, followed by **3-2c**. Colourless solid. Yield (4 mmol setup, 6 equiv. LiCl): **3-2c** 725 mg (75%).
R_f(hexane/EtOAc 5:1) = 0.28, R_f(hexane/EtOAc 2:1) = 0.60. - m.p. 21-22 °C. - ^{1}H NMR (200 MHz): δ = 1.11 (s, 3H, NCC*H$_3$*), 1.17 (s, 3H, NCC*H$_3$*), 1.23 (m+s, 4H, NCC*H$_3$*, NCCH$_2$C*H$_2$*CH$_2$CN), 1.33 (s, 3H, NCC*H$_3$*), 1.48 (br. s, 5H, NCC*H$_2$*C*H$_2$*C*H$_2$*CN), 2.29 (m, 1H, C*H$_2$*CHO), 2.67 (m, 1H, C*H$_2$*CHO), 4.08 (ddd, *J* = 10.8, 9.2, 5.7 Hz, 1H, C*H$_2$*O), 4.33 (dt, *J* = 8.8, 1.7 Hz, 1H, C*H$_2$*O), 4.71 (dd, *J* = 10.8, 7.9 Hz, 1H, C*H*OTMP). - ^{13}C NMR (50 MHz): δ = 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.2 (q, NC*C*H$_3$), 31.5 (t, *C*H$_2$CHOTMP), 32.3 (q, NC*C*H$_3$), 34.2 (q, NC*C*H$_3$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.4 (s, N*C*CH$_3$), 61.0 (s, N*C*CH$_3$), 64.0 (t, *C*H$_2$O), 80.3 (d, *C*HOTMP), 174.2 (s, CO). - IR (ATR): $\tilde{\nu}$ = 2972 (w), 2930 (w), 1781 (s), 1450 (w), 1375 (w), 1361 (w), 1261 (w), 1216 (m), 1180 (w), 1157 (s), 1132 (w), 1102 (s), 1020 (s), 992 (s), 974 (w), 951 (m), 919 (w), 711 (w), 543 (w) cm^{-1}. - MS (CI, pos.) *m/z* (%): 242 (72) [M+H$^+$], 226 (22) [M+H$^+$–CH$_3$], 156 (100) [TEMPO$^+$]. - Combustion analysis: $C_{13}H_{23}NO_3$ (241.33): calc. C 64.70, H 9.61, N 5.80; found: C 64.35, H 10.02, N 5.88.

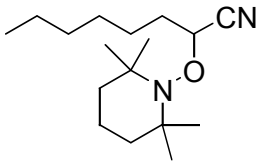
2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)phenylacetonitrile 3-5a



Flash chromatography (hexane/ethyl acetate 80:1, gradient to 50:1) gave ferrocene, followed by **3-5a**. Yellow oily solid, which turns to dark yellow or orange during a few hours at room

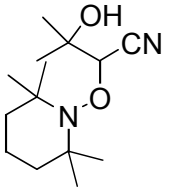
temperature, unstable to light and heat. Yield (5 mmol setup): 0.94 g (69%). Yield (3 mmol setup): 0.76 g (93%). Yield (5 mmol setup, 4.7 equiv. LiCl): 1 g (73%). R_f = 0.5 (hexane/EtOAc 10:1). - ^{1}H NMR (200 MHz): δ = 0.94 (s, 3H, NCC*H*$_3$), 1.02 (s, 3H, NCC*H*$_3$), 1.11 (s, 3H, NCC*H*$_3$), 1.21-1.59 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.41 (s, 3H, NCC*H*$_3$), 5.50 (s, 1H, CHON), 7.29-7.44 (m, 5H, Ph). - ^{13}C NMR (50 MHz): δ = 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.4 (q, NC*C*H$_3$), 20.5 (q, NC*C*H$_3$), 33.8 (q, NC*C*H$_3$), 34.6 (q, NC*C*H$_3$), 40.0 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 60.3 (s, N*C*CH$_3$), 60.9 (s, N*C*CH$_3$), 76.7 (d, CHON), 118.9 (s, *C*N), 127.2 (d, Ph), 128.9 (d, Ph), 129.4 (d, Ph), 134.9 (s, Ph). - IR (film): $\tilde{\nu}$ = 3070, 2971, 2942, 2874, 2214, 1687, 1602, 1583, 1548, 1451, 1382, 1315, 1271, 1175, 1120, 1070, 1025, 935, 793, 710 cm^{-1}. - MS (+ESI): *m/z* (%) = 295 (100) [M+Na$^+$], 273 (40) [M+H$^+$], 179 (41) [TEMPO+Na$^+$], 158 (21) [TEMPOH$_2^+$], 142 (3) [TMPH$_2^+$]. - Combustion analysis: $C_{17}H_{24}N_2O$ (272.39): calc. C 74.96, H 8.88, N 10.28; found C 75.16, H 8.88, N 10.21.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)capronitrile 3-5b



Flash chromatography (hexane/EtOAc 100:1, gradient to 2:1) gave ferrocene, followed by a mixture of ferrocene and **3-5b**, which was further purified. Yield (3 mmol setup): 661 mg (78%). Yield (5 mmol setup, 4.7 equiv. LiCl): 1.43 g (92%). The NMR data were in agreement with those from literature.[25] Pale yellow oil. R_f = 0.64 (hexane/EtOAc 10:1). - ^{1}H NMR (200 MHz): δ = 0.83 (t, *J* = 6.4 Hz, 3H, C*H*$_3$CH$_2$), 1.02 (s, 3H, NCC*H*$_3$), 1.04 (s, 3H, NCC*H*$_3$), 1.10 (s, 3H, NCC*H*$_3$), 1.16-1.66 (m, 17H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_3$(C*H*$_2$)$_4$, NCC*H*$_3$), 1.77 (m, 2H, C*H*$_2$CH), 4.52 (t, *J* = 6.5 Hz, 1H, C*H*OTMP). - ^{13}C NMR (50 MHz): δ = 14.0 (q, *C*H$_3$CH$_2$), 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.2 (q, NC*C*H$_3$), 20.4 (q, NC*C*H$_3$), 22.4 (t), 24.7 (t, *C*H$_2$), 28.8 (t, *C*H$_2$), 31.5 (t, *C*H$_2$), 32.9 (t, *C*H$_2$), 33.6 (q, NC*C*H$_3$), 34.0 (q, NC*C*H$_3$), 39.9 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.8 (s, N*C*CH$_3$), 60.8 (s, N*C*CH$_3$), 74.3 (d, *C*HOTMP), 119.7 (*C*N).

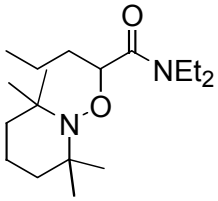
3-Hydroxy-3-methyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butyronitrile 3-5c



Deprotonation with 2.3 equiv. LDA at –78 - –50 °C for 35 min. Flash chromatography (hexane/EtOAc 20:1, gradient to 2:1) gave ferrocene, followed by **3-5c**. Yield 530 mg (99%)

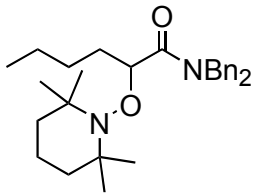
as a colourless solid. m.p. 22-23 °C. - R_f = 0.34 (hexane/EtOAc 5:1). - ^{1}H NMR (200 MHz): δ = 1.11 (s, 3H, NCC*H*$_3$), 1.17 (s, 3H, NCC*H*$_3$), 1.24 (s, 3H, NCC*H*$_3$), 1.34 (s, 3H, NCC*H*$_3$), 1.41 (s, 6H, HOC(C*H*$_3$)$_2$), 1.16-1.60 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 2.25 (br. s, 1H, O*H*), 4.59 (s, 1H, C*H*ON). - ^{13}C NMR (50 MHz): δ = 16.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.9 (q, NC*C*H$_3$), 24.8 (q, (*C*H$_3$)$_2$COH), 24.9 (q, (*C*H$_3$)$_2$COH), 33.0 (q, NC*C*H$_3$), 33.3 (q, NC*C*H$_3$), 39.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 39.5 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.6 (s, N*C*CH$_3$), 71.6 (s, (CH$_3$)$_2$*C*OH), 80.0 (d, *C*HON), 117.7 (s, *C*N). - IR (film): $\tilde{\nu}$ = 3431, 3338, 3011, 2976, 2938, 2871, 2250, 1465, 1382, 1363, 1259, 1235, 1182, 1133, 1070, 1003, 953, 913, 895, 808, 708 cm^{-1}. - MS (ESI): *m/z* (%) = 531 (37) [2M+Na$^+$], 277 (100) [M+Na$^+$], 179 (43) [TEMPO+Na$^+$]. - Combustion analysis: $C_{14}H_{26}N_2O_2$ (254.37): calc. C 66.10, H 10.30, N 11.01; found C 65.99, H 10.33, N 11.15.

***N,N*-Diethyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)pentanoic amide 3-5d**



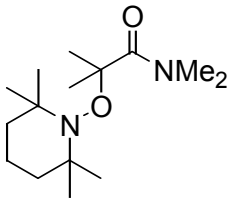
Flash chromatography (hexane/EtOAc 20:1, gradient to 2:1) gave ferrocene, followed by **3-5d**. Yield 589 mg (94%) as a pale yellow oil. R_f = 0.66 (hexane/EtOAc 2:1). - ^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$C*H*$_3$), 0.98 (s, 3H, NCC*H*$_3$), 1.02 (s, 3H, NCC*H*$_3$), 1.06 (t, *J* = 7.1 Hz, 3H, NCH$_2$C*H*$_3$), 1.09 (s, 3H, NCC*H*$_3$), 1.16 (s, 3H, NCC*H*$_3$), 1.17 (t, *J* = 7.1 Hz, 3H, NCH$_2$C*H*$_3$), 1.19 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 1.13-1.49 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.67-1.85 (m, 2H, CHC*H*$_2$), 3.26 (m, 2H, NC*H*$_2$), 3.35 (dq, *J* = 13.7, 6.9 Hz, 1H, NC*H*$_2$), 3.81 (dq, *J* = 14.6, 7.3 Hz, 1H, NC*H*$_2$), 4.41 (dd, *J* = 10.0, 4.7 Hz, 1H, C*H*ON). - ^{13}C NMR (100 MHz): δ = 12.4 (q, CH$_2$CH$_2$*C*H$_3$), 14.3 (q, NCH$_2$*C*H$_3$), 14.6 (q, NCH$_2$*C*H$_3$), 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.6 (t, CH$_3$*C*H$_2$CH$_2$), 19.9 (q, NC*C*H$_3$), 20.2 (q, NC*C*H$_3$), 32.9 (q, NC*C*H$_3$), 33.3 (q, NC*C*H$_3$), 34.4 (t, *C*H$_2$CHON), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.3 (t, *C*H$_2$N), 40.4 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 41.5 (t, *C*H$_2$N), 59.0 (s, N*C*CH$_3$), 60.4 (s, N*C*CH$_3$), 81.4 (d, *C*HON), 172.3 (s, *C*O). - IR (film): $\tilde{\nu}$ = 2964, 2933, 2874, 1652, 1463, 1455, 1432, 1377, 1362, 1259, 1133, 1123, 1023 cm^{-1}. - MS (+CI): *m/z* (%) = 313 (100) [M+H$^+$], 189 (6), 158 (17) [TEMPOH$_2^+$], 142 (38) [TMPH$_2^+$], 126 (18), 116 (9). - Combustion analysis: $C_{18}H_{36}N_2O_2$ (312.49): calc. C 69.18, H 11.61, N 8.96; found C 69.44, H 11.80, N 9.17.

***N,N*-Dibenzyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)hexanoic amide 3-5e**



Flash chromatography (hexane/EtOAc 80:1, gradient to 5:1) gave ferrocene, followed by **3-5e**. Yield 667 mg (74 %) as a pale yellow solid. m.p. 49-52 °C. - R_f = 0.42 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 0.87 (t, *J* = 6.9 Hz, 3H, C*H*$_3$CH$_2$), 0.91 (s, 3H, NCC*H*$_3$), 1.05 (s, 3H, NCC*H*$_3$), 1.09 (s, 6H, NCC*H*$_3$), 1.13-1.30 (m, 5H, CH$_3$C*H*$_2$C*H*$_2$, NCCH$_2$C*H*$_2$CH$_2$CN), 1.32-1.51 (m, 5H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.88 (m, 2H, C*H*$_2$CHO), 4.49 (d, *J* = 14.1 Hz, 1H, C*H*$_2$N), 4.59 (m, 3H, C*H*$_2$N, C*H*ON), 4.96 (d, *J* = 17.0 Hz, 1H, C*H*$_2$N), 7.29 (m, 10H, Ph). - ^{13}C NMR (100 MHz): δ = 13.2 (q, *C*H$_3$CH$_2$), 16.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.3 (q, NC*C*H$_3$), 19.6 (q, NC*C*H$_3$), 22.1 (t, CH$_3$*C*H$_2$), 26.8 (t, *C*H$_2$CH$_2$CHO), 31.2 (t, *C*H$_2$CHO), 32.4 (q, NC*C*H$_3$), 32.8 (q, NC*C*H$_3$), 39.6 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 47.6 (t, NCH$_2$), 48.6 (t, NCH$_2$), 58.7 (s, N*C*CH$_3$), 59.5 (s, N*C*CH$_3$), 81.4 (d, *C*HON), 126.1 (d, Ph), 126.64 (d, Ph), 126.65 (d, Ph), 127.5 (d, Ph), 127.9 (d, Ph), 128.8 (d, Ph), 136.0 (s, Ph), 136.1 (s, Ph), 172.4 (s, *C*O). - IR (film): $\tilde{\nu}$ = 2928, 2871, 1651, 1495, 1453, 1426, 1376, 1361, 1241, 1203, 1182, 1132, 1079, 1028, 1008, 988, 974, 956, 916, 732, 698 cm^{-1}. - MS (+ESI): *m/z* (%) = 451 (100) [M+H$^+$], 317 (5). - HRMS: $C_{29}H_{43}N_2O_2^+$: calc. 451.3325; found 451.3319. - Combustion analysis: $C_{29}H_{42}N_2O_2$ (450.66): calc. C 77.29, H 9.39, N 6.22; found C 77.33, H 9.48, N 6.00.

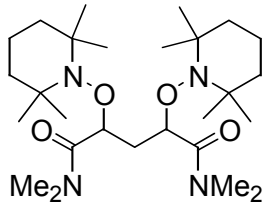
***N,N*-Dimethyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)isobutyramide 3-5f**



Flash chromatography (hexane/EtOAc 40:1, gradient to 2:1) afforded ferrocene, followed by residual TEMPO and **3-5f**. Yield 70 mg (13%) as a pale yellow oil. Yield (4.7 equiv. LiCl, deprotonation at –78 - –50 °C for 75 min): 30 mg (5%): R_f = 0.59 (hexane/EtOAc 2:1). - ^{1}H NMR (400 MHz): δ = 1.04 (s, 6H, NCC*H*$_3$), 1.10 (s, 6H, NCC*H*$_3$), 1.13-1.55 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.52 (s, 6H, (C*H*$_3$)$_2$CON), 2.94 (s, 3H, N(C*H*$_3$)$_2$), 3.39 (s, 3H, N(C*H*$_3$)$_2$). - ^{13}C NMR (100 MHz): δ = 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 21.5 (q, NC*C*H$_3$), 25.5 (q, (*C*H$_3$)$_2$CON), 33.3 (q, NC*C*H$_3$), 37.2 (q, N(*C*H$_3$)$_2$), 38.2 (q, N(*C*H$_3$)$_2$), 40.3 (t,

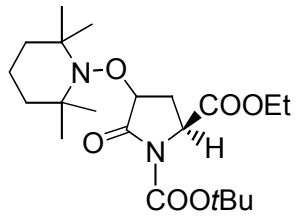
NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.4 (s, N*C*CH$_3$), 83.5 (s, (CH$_3$)$_2$*C*ON), 174.8 (s, *C*O). - IR (film): $\tilde{\nu}$ = 2974, 2934, 2932, 1643, 1472, 1382, 1362, 1260, 1184, 1182, 1145, 1119, 923, 827 cm^{-1}. - MS (+ESI): *m/z* (%) = 833 (93) [3M+Na$^+$], 563 (83) [2M+Na$^+$], 412 (27) [M+TMPH$_2^+$], 271 (100) [M+H$^+$]. - Combustion analysis: $C_{15}H_{30}N_2O_2$ (270.41): calc. C 66.62, H 11.18, N 10.36; found C 66.58, H 10.78, N 9.56.

2,4-Bis(2,2,6,6-tetramethylpiperidin-1-yloxy)-*N,N,N'N'*-tetramethylglutardiamide 3-5h



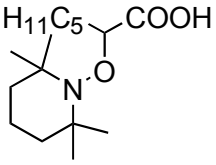
Flash chromatography (hexane/EtOAc 30:1, gradient to 1:2) afforded ferrocene, followed by residual TEMPO, and finally **3-5h**. Yield (using 2.0 equiv. TEMPO, 4.7 equiv. LiCl) 230 mg (23%, *d,l:meso* 4:1); yield (using 2.1 equiv. TEMPO, 6 equiv. LiCl) 280 mg (28%, *d,l:meso* 4:1) as a colourless solid. m.p. 21-22 °C. - R_f = 0.20 (hexane/EtOAc 2:1). - IR (film): $\tilde{\nu}$ = 2932, 2873, 1644, 1499, 1466, 1398, 1377, 1361, 1334, 1261, 1132, 1106, 1017, 982, 956, 910, 877, 793, 708, 656 cm^{-1}. - MS (+ESI): *m/z* (%) = 1015 (10) [2M+Na$^+$], 519 (100) [M+Na$^+$], 223 (23). - $C_{27}H_{52}N_4O_4$ (496.73): calc. C 65.29, H 10.55, N 11.28; found C 65.19, H 10.66, N 10.81. - *d,l*-**3-5h**: ^{1}H NMR (400 MHz): δ = 0.97 (s, 6H, NCC*H$_3$*), 1.04 (s, 6H, NCC*H$_3$*), 1.09 (s, 6H, NCC*H$_3$*), 1.20 (s, 6H, NCC*H$_3$*), 1.21-1.54 (m, 12H, NCC*H$_2$*C*H$_2$*C*H$_2$*CN), 2.22 (dt, *J* = 13.6, 3.4 Hz, 1H, CHC*H$_2$*CH), 2.68 (dt, *J* = 13.6, 9.5 Hz, 1H, CHC*H$_2$*CH), 2.84 (s, 6H, N(C*H$_3$*)$_2$), 3.21 (s, 6H, N(C*H$_3$*)$_2$), 4.72 (dd, *J* = 9.5, 3.4 Hz, 2H, C*H*CH$_2$C*H*). - ^{13}C NMR (100 MHz): δ = 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.1 (q, NC*C*H$_3$), 20.3 (q, NC*C*H$_3$), 32.6 (q, NC*C*H$_3$), 33.3 (q, NC*C*H$_3$), 33.7 (t, CH*C*H$_2$CH), 35.7 (q, N(*C*H$_3$)$_2$), 37.4 (q, N(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.5 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 59.3 (s, N*C*CH$_3$), 60.4 (s, N*C*CH$_3$), 79.3 (d, *C*HON), 171.9 (s, *C*O). - *meso*-**3-5h**: ^{1}H NMR (400 MHz): δ = 0.94 (s, 6H, NCC*H$_3$*), 1.04 (s, 6H, NCC*H$_3$*), 1.09 (s, 6H, NCC*H$_3$*), 1.19 (s, 6H, NCC*H$_3$*), 1.21-1.54 (m, 12H, NCC*H$_2$*C*H$_2$*C*H$_2$*CN), 2.43 (dd, *J* = 9.1, 6.4 Hz, 2H, CHC*H$_2$*CH), 2.88 (s, 6H, N(C*H$_3$*)$_2$), 3.19 (s, 6H, N(C*H$_3$*)$_2$), 4.32 (dd, *J* = 9.0, 6.5 Hz, 2H, C*H*CH$_2$C*H*). - ^{13}C NMR (100 MHz): δ = 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.9 (q, NC*C*H$_3$), 20.3 (q, NC*C*H$_3$), 32.3 (q, NC*C*H$_3$), 33.1 (q, NC*C*H$_3$), 34.1 (t, CH*C*H$_2$CH), 35.8 (q, N(*C*H$_3$)$_2$), 37.4 (q, N(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.5 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 59.2 (s, N*C*CH$_3$), 60.4 (s, N*C*CH$_3$), 79.1 (d, *C*HON), 172.0 (s, *C*O).

(2*S*,4*R*)- and (2*S*,4*S*)-Ethyl 1-(*tert*-butyloxycarbonyl)-5-oxo-4-(2,2,6,6-tetramethylpiperidinyl-1-yloxy)pyrrolidin-2-carboxylate 3-5i:



To a solution of (*S*)-**3-4i** (257 mg, 1 mmol) in dry THF (10 mL) was added a LiHMDS solution (1.05 mL, 1.05 mmol, 1.0*M* in THF) at –78 °C. After stirring for 0.5 h, **1-2** (172 mg, 1.1 mmol) was added to the reaction mixture. Stirring was continued for 5 min until it dissolved. Ferrocenium hexafluorophosphate **1-3** was added in portions at –78 °C until the solution remained dark blue for at least 5 min. Workup was performed according to the general procedure (vide supra). Flash chromatography (hexane/ethyl acetate 40:1, gradient to 1:1) afforded starting from a polarity 10:1 110 mg of (2*S*,4*R*)-**3-5i**, followed by 80 mg of a mixture of (2*S*,4*R*)-**3-5i** and (2*S*,4*S*)-**3-5i**, and finally 100 mg of (2*S*,4*S*)-**3-5i** as colourless solids. Yield 290 mg (70%), (2*S*,4*R*)-**3-5i**:(2*S*,4*S*)-**3-5i** 1:1.2. HPLC investigations on a DAICEL-OD chiral column showed that (2*S*,4*R*)-**3-5i** and (2*S*,4*S*)-**3-5i** are enantiomerically pure. (2*S*,4*R*)-**3-5i**: $[\alpha]^{20}_{D}$ = +4.5 ° (c = 0.353, $CHCl_3$), R_f = 0.44 (hexane/EtOAc 5:1); (2*S*,4*S*)-**3-5i**: $[\alpha]^{20}_{D}$ = –24.4 ° (c = 0.468, $CHCl_3$), R_f = 0.32 (hexane/EtOAc 5:1). The NMR data are in agreement with those reported earlier.[25] Combustion analysis: $C_{21}H_{36}N_2O_6$ (412.52): calc. C 61.14, H 8.80, N 6.79; found C 60.92, H 8.90, N 6.54.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)heptanoic acid 3-7

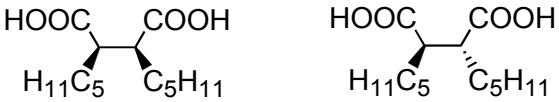


A solution of *n*BuLi (2.75 mL, 4.4 mmol, 1.6 *M* in hexane) was added at −78 °C to a solution of anhydrous LiCl (400 mg, 9.4 mmol) and dry diethyl amine (0.455 mL, 321 mg, 4.4 mmol) in dry THF (20 mL). The reaction mixture was stirred at −78 °C for 10 min and at 0 °C for 20 min. The acid (0.284 mL, 2 mmol) was added via syringe at −78 °C. After stirring at the same temperature for 10 min and at 0 °C for 1 h, the reaction was cooled to −78 °C and TEMPO (374 mg, 2.4 mmol) was added. Stirring was continued for 5 min, and ferrocenium hexafluorophosphate (0.99 g, 3 mmol) was added in portions at −78 °C during 10 min until a blue colour persisted in the mixture. The reaction mixture was stirred at −78 °C for 10 min and quenched with 30 mL water. The organic layer was extracted twice with water. The

combined aqueous layers were acidified with conc. HCl (3.5 mL) and extracted with diethyl ether. The combined ethereal layers were washed with water and brine, dried over Na_2SO_4 and the solvent was removed in vacuum. Flash chromatography (hexane/EtOAc 10:1, gradient to 2:1) afforded ferrocene, followed by residual **1-2**, 80 mg of a mixture of **3-6** and **3-9**, and 360 mg of a mixture of products **3-7** and *meso*-**3-8** at polarity 2:1. Yield based on the NMR spectra: 57 mg (22%) of recovered **3-6**, 23 mg (9%) of **3-9**, 291 mg (51%) of **3-7**, and 36 mg (14%) of *meso*-**3-8**. Further purification of the product allowed the analytical characterisation.

3-7: R_f = 0.35 (hexane/EtOAc 2:1). - ^{1}H NMR (400 MHz): δ = 0.84 (t, *J* = 7.0 Hz, 3H, $CH_2CH_2CH_3$), 1.19 (s, 3H, $NCCH_3$), 1.21 (s, 3H, $NCCH_3$), 1.24 (s, 3H, $NCCH_3$), 1.28 (m, 4H, $CH_3CH_2CH_2$), 1.29 (s, 3H, $NCCH_3$), 1.44 (m, 3H, $CHCH_2CH_2$, $NCCH_2CH_2CH_2CN$), 1.61 (m, 5H, $NCCH_2CH_2CH_2CN$), 1.74 (m, 1H, $CHCH_2$), 2.03 (m, 1H, $CHCH_2$), 4.37 (dd, *J* = 8.5, 4.0 Hz, 1H, CHON), 14.58 (br. s, 1H, COOH). - ^{13}C NMR (100 MHz): δ = 13.7 (q, CH_2CH_3), 16.1 (t, $NCCH_2CH_2CH_2CN$), 20.7 (q, $NCCH_3$), 22.1 (t, CH_2CH_3), 25.0 (t, $CHCH_2CH_2$), 30.0 (q, $NCCH_3$), 30.9 (q, $NCCH_3$), 31.2 (t, $CH_3CH_2CH_2$), 31.6 (t, $CHCH_2$), 38.9 (t, $NCCH_2CH_2CH_2CN$), 39.0 (t, $NCCH_2CH_2CH_2CN$), 62.4 (s, $NCCH_3$), 62.7 (s, $NCCH_3$), 80.0 (d, CHON), 174.0 (s, COOH). - IR (film): $\tilde{\nu}$ = 3350-2450 (br. w), 2930, 2870, 1718, 1464, 1376, 1362, 1239, 1211, 1180, 1132, 1039, 957, 793, 712 cm^{-1}. - MS (+CI): *m/z* (%) = 286 (23) [$M+H^+$], 158 (9) [$TEMPOH_2^+$], 142 (100) [$TMPH_2^+$], 126 (10), 111 (11), 98 (9), 75 (9), 69 (20), 61 (28). - HRMS (+ESI): $C_{16}H_{31}NO_3Na^+$: calc. 308.2202; found 308.2199. - Combustion analysis: $C_{16}H_{31}NO_3$ (285.42): calc. C 67.33, H 10.95, N 4.91; found C 67.04, H 11.10, N 4.90.

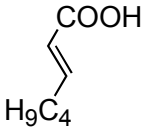
meso/d,l-**Dodecan-6,7-dicarboxylic acids 3-8**



The dimers **3-8** were isolated as a mixture together with residual **3-6** and the disproportionation product **3-9**.

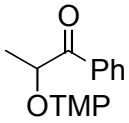
meso-**3-8**: ^{1}H NMR (200 MHz): δ = 0.89 (m, 6H, CH_2CH_3), 1.28-1.62 (m, 16H, $CH_2CH_2CH_2CH_2CH_3$), 2.66 (m, 2H, CHCOOH), 11.92 (br. s, 2H, COOH). - ^{13}C NMR (50 MHz): δ = 14.1 (q, CH_2CH_3), 22.1 (t, CH_3CH_2), 27.0 (t, CH_2), 30.6 (t, CH_2), 31.5 (t, $CHCH_2$), 48.0 (d, CHCOOH), 178.1 (s, COOH). - *d,l*-**3-8**: Detectable resonances: ^{1}H NMR (200 MHz): δ = 0.89 (m, 6H, CH_2CH_3), 1.28-1.62 (m, 16H, $CH_2CH_2CH_2CH_2CH_3$), 2.71 (m, 2H, CHCOOH), 11.92 (br. s, 2H, COOH). - ^{13}C NMR (50 MHz): δ = 22.4 (t, CH_3CH_2), 26.3 (t, CH_2), 28.7 (t, CH_2), 31.6 (t, $CHCH_2$), 46.0 (d, CHCOOH), 180.7 (s, COOH).

***(E)*-2-Heptenoic acid 3-9**



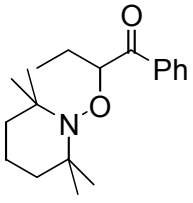
R_f = 0.57 (hexane/EtOAc 2:1). - ^{1}H NMR (200 MHz): δ = 0.90 (m, 3H, CH_2CH_3), 1.29-1.53 (m, 4H, $CH_3CH_2CH_2$), 2.23 (q, *J* = 6.7 Hz, 2H, CH_2CH), 5.82 (d, *J* = 15.6 Hz, 1H, *CH*COOH), 7.12 (dt, *J* = 15.6, 7.0 Hz, 1H, *CH*=CHCOOH), 11.40 (br. s, 1H, COO*H*). - ^{13}C NMR (50 MHz): δ = 13.7 (q, CH_2CH_3), 22.2 (t, CH_2CH_3), 29.9 (t, $CHCH_2CH_2$), 31.9 (t, $=CHCH_2$), 120.6 (d, =*C*HCOOH), 152.5 (d, $=CHCH_2$), 172.3 (s, *C*OOH).

1-Phenyl-2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)propan-1-one 3-11a



Flash chromatography (hexane/ethyl acetate 80:1, gradient to 1:2) afforded ferrocene, followed by **3-11a,** residual **1-2**, and *d,l/meso*-**3-10a**. Further purification provided pure **3-11a**. Yield Method A (2 mmol setup): **3-11a** 175 mg (30%), *d,l/meso*-**3-10a** 158 mg (59%) 10.5:1; Method B-2 (2 mmol setup): **3-11a** 457 mg (78%), *d,l/meso*-**3-10a** 60 mg (21%) 5:1; Method C (2 mmol setup): **3-11a** 307 mg (52%), *d,l/meso*-**3-10a** 129 mg (49%) 6:1. Colourless solid. m.p. 69-71 °C. - R_f = 0.63 (hexane/EtOAc 10:1). - The NMR data are in agreement with those reported in the literature.[25]

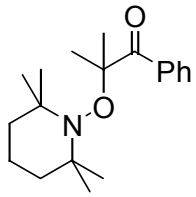
1-Phenyl-2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)butan-1-one 3-11b



Flash chromatography (hexane/EtOAc 80:1, gradient to 5:1) afforded ferrocene, followed by **3-11b** and *d,l/meso*-dimer **3-12b**. Yields (2 mmol setup): **3-11b** 230 mg (38%), *d,l/meso*-**3-12b** 161.5 mg (55%) 45:1. Yields (5 mmol setup, 6 equiv. LiCl): **3-11b** 1.03 g (70%), *d,l*-**3-12b** 242 mg (30%). Colourless solid. m.p. 63-65 °C. - R_f = 0.50 (hexane/EtOAc 10:1). - ^{1}H NMR (200 MHz): δ = 0.79 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.87 (s, 3H, $NCCH_3$), 1.05 (s, 3H, $NCCH_3$), 1.15-1.49 (m, 6H, $NCCH_2CH_2CH_2CN$), 1.20 (s, 3H, $NCCH_3$), 1.30 (s, 3H, $NCCH_3$), 2.02 (m, 2H, CH_2CHON), 4.86 (dd, *J* = 8.4, 5.4 Hz, 1H, $CHCH_2$), 7.50 (m, 3H, *m,p*-Ph), 8.10

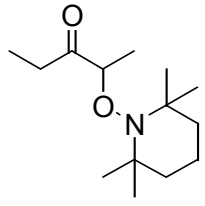
(dd, J = 8.3, 1.7 Hz, 2H, *o*-Ph). - ^{13}C NMR (50 MHz): δ = 9.1 (q, CH_2CH_3), 17.1 (t, $NCCH_2CH_2CH_2CN$), 20.2 (q, $NCCH_3$), 25.8 (t, CH_2CH_3), 33.6 (q, $NCCH_3$), 33.8 (q, $NCCH_3$), 40.3 (t, $NCCH_2CH_2CH_2CN$), 59.7 (s, $NCCH_3$), 90.8 (d, CHON), 128.4 (d, Ph), 129.1 (d, Ph), 132.8 (d, Ph), 136.0 (s, Ph), 201.2 (s, CO). - IR (film): $\tilde{\nu}$ = 2971, 2933, 2875, 1679, 1597, 1448, 1375, 1361, 1265, 1241, 1213, 1182, 1133, 1045, 1015, 988, 962, 914, 850, 794, 777, 698 cm^{-1}.- MS (+CI): *m/z* (%) = 304 (100) [M+H$^+$], 157 (9) [TEMPO+H$^+$], 156 (62) [TEMPO$^+$], 142 (7) [$TMPH_2^+$], 105 (12) [PhC=O$^+$]. - HRMS (ESI): $C_{19}H_{29}NO_2Na^+$: calc. 326.2096; found 326.2090. - Combustion analysis: $C_{19}H_{29}NO_2$ (303.44): calc. C 75.21, H 9.63, N 4.62; found C 75.27, H 9.77, N 4.67.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)isobutyrophenone 3-11c



Flash chromatography (hexane/EtOAc 80:1, gradient to 20:1) afforded a mixture of ferrocene, **3-11c** and isobutyrophenone **3-10c**, followed by an inseparable mixture of **3-11c**, **3-10c**, and **1-2** with R_f = 0.3 (hexane/EtOAc 10:1). Yield: 111 mg (18%), recovered **3-10c** 184 mg (62%). Pale yellow oil. R_f = 0.54 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 0.988 (s, 6H, $NCC\mathit{H_3}$), 0.990 (s, 6H, $NCC\mathit{H_3}$), 1.25-1.59 (m, 6H, $NCC\mathit{H_2}C\mathit{H_2}C\mathit{H_2}CN$), 1.62 (s, 6H, $OC(CH_3)_2$), 7.41-7.56 (m, 3H, *m,p*-Ph), 8.30 (d, J = 7.1 Hz, 2H, *o*-Ph). - ^{13}C NMR (100 MHz): δ = 16.7 (t, $NCCH_2CH_2CH_2CN$), 20.8 (q, $NCCH_3$), 25.4 (q, $OC(CH_3)_2$), 33.1 (q, $NCCH_3$), 40.1 (t, $NCCH_2CH_2CH_2CN$), 59.1 (s, $NCCH_3$), 86.9 (s, CON), 127.6 (d, Ph), 130.6 (d, Ph), 131.9 (d, Ph), 134.7 (s, Ph), 201.8 (s, C=O). - MS (+ESI) (mixture of **3-11c**/**3-10c** 3.3:1): *m/z* (%) = 629 (34) [2M+Na$^+$], 482 (26), 473 (26), 326 (100) [M+Na$^+$], 284 (57), 179 (44) [TEMPO+Na$^+$], 158 (39) [$TEMPOH_2^+$], 142 (19) [TMPH+H$^+$]. - HRMS: $C_{19}H_{29}NO_2Na^+$: calc. 326.2096; found 326.2094.

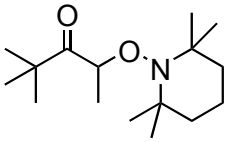
2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)pentan-3-one 3-11d



Flash chromatography (hexane/EtOAc 40:1, gradient to 2:1) gave ferrocene, followed by **3-11d**. Yield 380 mg (79%) as a pale yellow oil. R_f = 0.40 (hexane/EtOAc 5:1). - ^{1}H NMR (400

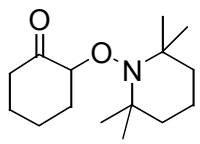
MHz): δ = 0.92 (br. s, 3H, NCC*H*$_3$), 0.99 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$CO), 1.04 (br. s, 3H, NCC*H*$_3$), 1.09 (br. s, 6H, NCC*H*$_3$), 1.18-1.52 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.25 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CHCO), 2.48 (dq, *J* = 18.5, 7.2 Hz, 1H, OCC*H*$_2$CH$_3$), 2.65 (dq, *J* = 18.5, 7.3 Hz, 1H, OCC*H*$_2$CH$_3$), 4.22 (q, *J* = 7.0 Hz, 1H, C*H*ON). - ^{13}C NMR (100 MHz): δ = 7.1 (q, CH$_2$*C*H$_3$), 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.0 (q, CH*C*H$_3$), 20.2 (q, NC*C*H$_3$), 31.3 (t, CH$_3$*C*H$_2$CO), 33.7 (q, NC*C*H$_3$), 34.2 (q, NC*C*H$_3$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.4 (s, N*C*CH$_3$), 59.9 (s, N*C*CH$_3$), 87.1 (d, *C*HON), 213.4 (s, *C*O). - IR (film): $\tilde{\nu}$ = 2975, 2933, 2874, 1717, 1456, 1375, 1361, 1260, 1242, 1209, 1184, 1133, 1093, 1045, 1018, 992, 958, 926, 881, 789, 713 cm^{-1}. - MS (+ESI): *m/z* (%) = 748 (6) [3M+Na$^+$+H], 704 (8), 660 (8), 615 (8), 505 (25) [2M+Na$^+$], 443 (7), 270 (6), 264 (68) [M+Na$^+$], 242 (7), 186 (29), 142 (100) [TMPH$_2^+$], 126 (26). - Combustion analysis: $C_{14}H_{27}NO_2$ (241.20): calc. C 69.66, H 11.27, N 5.80; found C 69.55, H 11.47, N 5.90.

2,2-Dimethyl-4-(2,2,6,6-tetramethylpiperidin-1-yloxy)pentan-3-one 3-11e



Flash chromatography (hexane/EtOAc 100:1, gradient to 20:1) afforded ferrocene, followed by **3-11e** and residual **1-2**. Yield 506 mg (94%) as a pale yellow oil. R_f = 0.54 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 0.97 (br. s, 3H, NCC*H*$_3$), 1.12 (br. s, 6H, NCC*H*$_3$), 1.18 (s, 9H, C(C*H*$_3$)$_3$), 1.19 (br. s, 3H, NCC*H*$_3$), 1.25-1.62 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.30 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 4.81 (q, *J* = 6.8 Hz, 1H, C*H*ON). - ^{13}C NMR (100 MHz): δ = 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.4 (q, CH*C*H$_3$), 20.3 (q, NC*C*H$_3$), 26.8 (q, C(*C*H$_3$)$_3$), 33.9 (q, NC*C*H$_3$), 40.3 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.3 (s, OC*C*(CH$_3$)$_3$), 59.7 (s, N*C*CH$_3$), 80.2 (d, *C*HON), 216.3 (s, CO). - IR (film): $\tilde{\nu}$ = 2971 (s), 2933 (s), 2872 (m), 1718 (s), 1477 (m), 1363 (s), 1133 (m), 1047 (m), 983 (s), 938 (m) cm^{-1}. - MS (+CI): *m/z* (%) = 270 (100) [M+H$^+$]. - HRMS (ESI): $C_{16}H_{32}NO_2^+$: calc. 270.2427; found 270.2428; $C_{16}H_{31}NO_2Na^+$: calc. 292.2247; found 292.2248. - Combustion analysis: $C_{16}H_{31}NO_2$ (269.42): calc. C 71.33, H 11.60, N 5.20; found C 71.61, H 11.77, N 5.46.

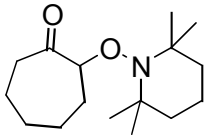
2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)cyclohexanone 3-11f[25]



Flash chromatography (hexane/ethyl acetate 50:1, gradient to 3:1) afforded ferrocene, followed by **3-11f**, and finally dimer **3-12f**. If necessary, a second purification was performed.

Yields: **3-11f** 430 mg (85%) and *d,l/meso*-**3-12f** 20 mg (9%, d.r. 2.5:1). With LiCl: **3-11f** 0.97 g (77%). With HMPA: **3-11f** 0.25 g (49%) impure, contains small amounts of unknown products. Pale yellow oil. R_f = 0.29 (hexane/EtOAc 10:1). - $C_{15}H_{27}NO_2$ (253.38): calc. C 71.10, H 10.74, N 5.53; found C 70.89, H 10.65, N 5.36.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)cycloheptanone 3-11g

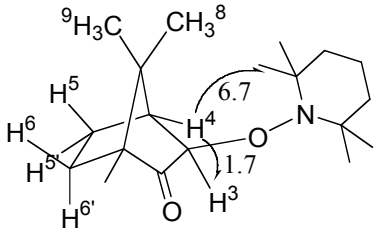


Flash chromatography (hexane/EtOAc 80:1, gradient to 10:1) gave ferrocene, followed by **3-11g**. Yield (5 mmol setup): 1.16 g (87%) as a pale yellow oil. m.p. 23-24 °C. - R_f = 0.48 (hexane/EtOAc 10:1). - ^{1}H-NMR (400 MHz): δ = 0.98 (s, 3H, NCCH_3), 1.15 (s, 9H, NCCH_3), 1.22-1.53 (m, 8H, CH_2CH$_2$CH$_2$C=O, CH_2CH$_2$CHO, NCCH_2CH_2CH_2CN), 1.63-1.81 (m, 4H, CH_2CH_2CH_2CH_2CHON), 1.96 (m, 2H, CH_2CH$_2$C=O, CH_2CHON), 2.34 (ddd, *J* = 15.0, 9.2, 5.2 Hz, 1H, CH_2C=O), 2.79 (ddt, *J* = 15.1, 6.0, 1.3 Hz, 1H, CH_2C=O), 4.31 (dd, *J* = 8.1, 3.2 Hz, 1H, C*H*ON). - ^{13}C-NMR (100 MHz): δ = 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.3 (q, NC*C*H$_3$), 23.4 (t, *C*H$_2$CH$_2$C=O), 24.5 (t, *C*H$_2$CH$_2$CHON), 28.3 (t, *C*H$_2$CH$_2$CH$_2$C=O), 30.4 (t, *C*H$_2$CHON), 33.7 (q, NC*C*H$_3$), 40.1 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 41.4 (t, *C*H$_2$C=O), 59.5 (s, N*C*CH$_3$), 92.4 (d, *C*HON), 213.8 (s, *C*=O). - IR: $\tilde{\nu}$ = 2999 (w), 2970 (m), 2929 (s), 2869 (w), 2679 (w), 1705 (s), 1452 (m), 1411 (w), 1376 (w), 1359 (m), 1262 (w), 1241 (w), 1208 (w), 1184 (w), 1134 (m), 1101 (w), 1083 (w), 1048 (m), 1018 (m), 990 (w), 957 (m), 932 (s), 854 (w), 831 (w), 790 (w) cm^{-1}. - MS (+CI): *m/z* (%) = 268 (100) [M+H$^+$], 156 (5) [TEMPO$^+$], 142 (3) [TMPH$_2^+$]. - HRMS (ESI): for $C_{16}H_{29}NO_2^+$ calc. 267.2192; found 267.2192. - Combustion analysis: $C_{16}H_{29}NO_2$ (267.41): calc. C 71.86, H 10.93, N 5.24; found C 71.61, H 11.16, N 5.46.

***(R)*-2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)camphor 3-11h:**

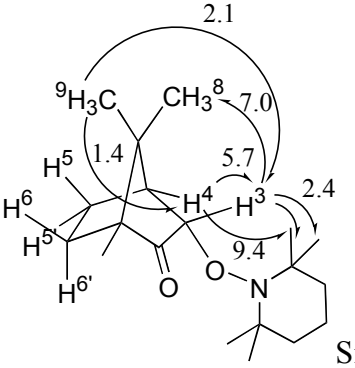
Flash chromatography (hexane/ethyl acetate 100:1, gradient to 5:1) afforded ferrocene, followed by a mixture of *endo*-**3-11h**, *exo*-**3-11h,** and sometimes *exo,exo*-dimer **3-12h** as colourless solids. Yield (1 mmol setup): **3-11h** 263 mg (85%, 2-*exo/endo* 1:1.1) and 2,2'-*exo,exo*-dimer **3-12h** 5 mg (2%). With LiCl (5 mmol setup): **3-11h** 1.49 g (95%, *exo/endo* 1.1:1). The following analyses were performed on diastereomeric mixture prior to further purification. IR (KBr): $\tilde{\nu}$ = 3010 (s), 2991 (s), 2965 (s), 2939 (s), 2890 (s), 2871 (s), 2848 (s), 1750 (s), 1470 (m), 1453 (m), 1391 (w), 1375 (s), 1360 (w), 1259 (w), 1181 (w), 1131 (m),

1063 (w), 1010 (s), 994 (s), 958 (w), 945 (m), 840 (w) cm^{-1}. - MS (EI) *m/z* (%): 307 (48) [M^+], 292 (42) [M^+–CH_3], 156 (100) [$TEMPO^+$], 142 (14) [$TMPH_2^+$], 123 (53) [M^+–TEMPO–CH_2=CH_2], 81 (14) [M^+–TEMPO–CH_2=CH_2–*i*Pr], 69 (11), 55 (19), 41 (18). - Combustion analysis: $C_{19}H_{33}NO_2$ (307.47): calc. C 74.22, H 10.82, N 4.56; found C 74.15, H 10.90, N 4.33.



Significant NOE contacts

***(R)*-2-*exo*-3-11h**: R_f = 0.43 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 0.86 (s, 3H, CH_2CCH_3), 0.88 (s, 3H, $CHCCH_3$), 0.95 (s, 3H, $CHCCH_3$), 1.06 (br. s, 3H, $NCCH_3$), 1.16 (br. s, 6H, $NCCH_3$), 1.23-1.42 (m, 6H, $NCCH_2CH_2CH_2CN$, CCH_2CH_2CH, $NCCH_3$), 1.42 (br. s, 4H, $NCCH_2CH_2CH_2CN$), 1.52 (m, 2H, CH_2CC=O, $NCCH_2CH_2CH_2CN$), 1.90 (m, 1H, CH_2CH_2CH), 2.43 (d, *J* = 4.9 Hz, 1H, $CHCHON$), 4.02 (s, 1H, $CHON$). - ^{13}C NMR (100 MHz): δ = 9.1 (q, CH_3CC=O), 17.1 (t, $NCCH_2CH_2CH_2CN$), 19.8 (q, $CHCCH_3$), 20.2 (q, $NCCH_3$), 20.8 (q, $CHCCH_3$), 25.0 (t, CH_2CHCH), 28.8 (t, CH_2CH_2CH), 32.1 (q, $NCCH_3$), 35.0 (q, $NCCH_3$), 40.4 ($NCCH_2CH_2CH_2CN$), 46.2 (s, $CHC(CH_3)_2$), 48.3 (d, $CHCHON$), 56.8 (s, CH_3CCO), 59.5 (s, $NCCH_3$), 61.5 (s, $NCCH_3$), 90.7 (d, $CHON$), 217.5 (s, C=O).



Significant NOE contacts

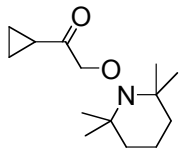
***(R)*-2-*endo*-3-11h**: m.p. 25-26 °C. - R_f = 0.51 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 0.81 (s, 3H, $CHC(CH_3)_2$), 0.85 (s, 3H, CH_2CCH_3), 0.93 (s, 3H, $CHCCH_3$), 1.06 (br. s, 3H, $NCCH_3$), 1.09 (br. s, 3H, $NCCH_3$), 1.17 (br. s, 3H, $NCCH_3$), 1.20-1.59 (m, 10H, $NCCH_2CH_2CH_2CN$, CCH_2CH_2CH, $NCCH_3$), 1.64 (m, 2H, CCH_2CH_2CH), 1.87 (m, 1H, CCH_2CH_2CH), 2.37 (t, *J* = 4.3 Hz, 1H, $CHCHON$), 4.46 (dd, *J* = 4.7, 1.1 Hz, 1H, $CHON$). - ^{13}C NMR (100 MHz): δ = 9.5 (q, CH_3CC=O), 17.0 (t, $NCCH_2CH_2CH_2CN$), 18.8 (q,

CHC*C*H$_3$), 18.8 (t, CH$_2$*C*H$_2$CH), 19.8 (q, CHC*C*H$_3$), 20.0 (q, NC*C*H$_3$), 20.1 (q, NC*C*H$_3$), 32.1 (t, C*C*H$_2$CH$_2$), 32.1 (q, NC*C*H$_3$), 34.2 (q, NC*C*H$_3$), 40.5 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.1 (s, CH*C*(CH$_3$)$_2$), 48.4 (d, *C*HCHON), 58.4 (s, CH$_3$*C*CO), 59.0 (s, N*C*CH$_3$), 62.0 (s, N*C*CH$_3$), 88.5 (d, *C*HON), 216.7 (s, C=O).

Oxygenation of alkyl methyl ketones 3-10i-k (general procedure)

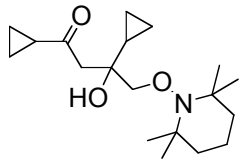
Ketone **3-10i-k** (2 mmol) was added via syringe to a solution of 2.6 mmol of LDA prepared from diisopropylamine (0.366 mL, 2.6 mmol) and BuLi (1.6*M* in hexane, 1.625 mL, 2.6 mmol) in 20 mL dry THF at −78 °C, and the mixture was stirred for the given time (Table 3.8). TEMPO **1-2** (343.2 mg, 2.2 mmol, 1.1 equiv.) was added. Subsequently, ferrocenium hexafluorophosphate (minimum 2 equiv.) was added in portions at −78 °C until a dark blue colour persisted in the reaction mixture for 15 to 20 minutes. The reaction mixture was quenched with 10 drops of water, diluted with diethyl ether and filtered through a pad of silica gel. The solvent was removed in vacuum and the crude product preadsorbed on silica gel was purified by column chromatography.

Cyclopropyl (2,2,6,6-tetramethylpiperidin-1-yloxy)methyl ketone 3-11i



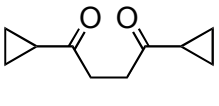
Flash chromatography (hexane/ethyl acetate 80:1, gradient to 5:1) afforded ferrocene, followed by **3-11i**, aldol addition/TEMPO trapping product **3-13i**, and an inseparable mixture of dimers **3-12i** and **3-12'i** in a 1:1 ratio. Yield deprotonation 20 min: **3-11i** 20 mg (4%), **3-13i** 159 mg (50%), **3-12i** 35 mg (20%), **3-12'i** 35 mg (22%). Yield with LiCl, deprotonation 10 min: **3-11i** 110 mg (23%) and **3-13i** 220 mg (68%). Pale yellow oils. R_f = 0.48 (hexane/EtOAc 10:1). - IR (film): $\tilde{\nu}$ = 3012, 2978, 2935, 2915, 2877, 2849, 1708, 1471, 1448, 1392, 1374, 1360, 1340, 1264, 1188, 1132, 1050, 1017, 995, 955, 928, 907, 858, 820, 774, 716 cm^{-1}. - ^{1}H NMR (200 MHz): δ = 0.93 (m, 2H, C*H*$_2$CHCO), 1.09 (m, 2H, C*H*$_2$CHCO), 1.17 (s, 12H, NCC*H*$_3$), 1.25-1.63 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 2.30 (m, 1H, CH$_2$C*H*CO), 4.51 (s, 2H, C*H*$_2$ON). - ^{13}C NMR (50 MHz): δ = 11.2 (t, CH*C*H$_2$), 17.0 (d, *C*HCO), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.2 (q, NC*C*H$_3$), 32.8 (q, NC*C*H$_3$), 39.6 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 60.0 (s, N*C*CH$_3$), 83.4 (t, *C*H$_2$ON), 208.6 (s, *C*O). - MS (+ESI): *m/z* (%) = 501 (39) [2M+Na$^+$], 262 (100) [M+Na$^+$], 179 (4) [TEMPO+Na$^+$]. - Combustion analysis: C$_{14}$H$_{25}$NO$_2$ (239.35): calc. C 70.25, H 10.53, N 5.85; found C 70.29, H 10.66, N 5.83.

2,4-Bis(cyclopropyl)-2-hydroxy-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)butan-4-one 3-13i

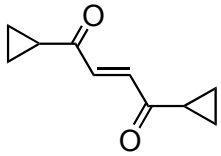


R_f = 0.34 (hexane/EtOAc 10:1). - IR (film): $\tilde{\nu}$ = 2975, 2933, 2875, 1717, 1455, 1376, 1361, 1260, 1242, 1184, 1133, 1091, 1018, 992, 959, 927, 882, 790, 713 cm^{-1}. - ^1H NMR (400 MHz): δ = 0.34 (m, 2H, C*H*$_2$C*H*$_2$CHCOH), 0.50 (m, 2H, C*H*$_2$C*H*$_2$CHCOH), 0.95 (m, 2H, C*H*$_2$C*H*$_2$CHC=O), 1.02-1.16 (m, 3H, CH$_2$C*H*COH, C*H*$_2$C*H*$_2$CHC=O), 1.12 (br. s, 9H, NCC*H*$_3$), 1.19 (br. s, 3H, NCC*H*$_3$), 1.22-1.62 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 2.03 (tt, *J* = 4.5, 7.8 Hz, 1H, CH$_2$C*H*C=O), 2.81 (A part of AB system, *J* = 16.3 Hz, 1H, COC*H*$_2$COH), 3.03 (B part of AB system, *J* = 16.3 Hz, 1H, COC*H*$_2$COH), 3.76 (AB system, *J* = 8.3 Hz, 2H, C*H*$_2$ON), 4.00 (br. s, 1H, OH). - ^{13}C NMR (100 MHz): δ = −0.2 (t, *C*H$_2$CHCOH), 0.2 (t, *C*H$_2$CHCOH), 11.4 (t, *C*H$_2$CHC=O), 11.9 (t, *C*H$_2$CHC=O), 16.9 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.0 (d, CH$_2$*C*HCOH), 20.2 (q, NC*C*H$_3$), 22.1 (d, CH$_2$*C*HC=O), 32.8 (q, NC*C*H$_3$), 32.9 (q, NC*C*H$_3$), 39.7 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 49.1 (t, HOC*C*H$_2$C=O), 59.9 (s, N*C*CH$_3$), 70.8 (s, *C*OH), 81.9 (t, *C*H$_2$ON), 213.2 (s, *C*O). - MS (+ESI): *m/z* (%) = 669 (10) [2M+Na$^+$], 583 (28), 346 (100) [M+Na$^+$], 271 (4). - Combustion analysis: $C_{19}H_{33}NO_3$ (323.47): calc. C 70.55, H 10.28, N 4.33; found C 70.60, H 10.33, N 4.48.

1,4-Bis(cyclopropyl)butan-1,4-dione 3-12i and 1,4-Bis(cyclopropyl)-2-buten-1,4-dione 3-12'i



3-12i



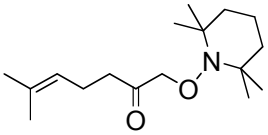
3-12'i

The dimers **3-12i** and **3-12'i** were isolated and analysed as an inseparable 1:1 mixture. R_f = 0.34 (hexane/EtOAc 5:1). - IR (film): $\tilde{\nu}$ = 3091, 3009, 2974, 2934, 1693, 1666, 1445, 1385, 1264, 1243, 1183, 1144, 1074, 1023, 980, 902, 816 cm^{-1}. - MS (+ESI): *m/z* (%) = 561 (39), 510 (24), 479 (30), 428 (100), 426 (22), 189 (100) [M(**3-12i**)+Na$^+$], 187 (8) [M(**3-12'i**)+Na$^+$], 167 (11) [M (**3-12i**)+H$^+$]. - HRMS: **3-12i** $C_{10}H_{14}O_2Na^+$: calc. 189.0891; found 189.0886. - HRMS: **3-12'i** $C_{10}H_{12}O_2Na^+$: calc. 187.0735; found 187.0730.

3-12i: ^{1}H NMR (400 MHz): δ = 0.88 (dt, *J* = 7.9, 3.3 Hz, 4H, C*H*$_2$C*H*$_2$CHCO), 1.06 (m, 4H, C*H*$_2$C*H*$_2$CHCO), 1.96 (tt, *J* = 7.8, 4.5 Hz, 2H, C*H*COCH$_2$), 2.86 (s, 4H, COC*H*$_2$C*H*$_2$CO). - ^{13}C NMR (100 MHz): δ = 10.6 (t, *C*H$_2$CHCO), 20.5 (d, CH$_2$*C*HCO), 36.4 (t, CO*C*H$_2$), 209.2 (s, *C*O).

3-12'i: ^{1}H NMR (400 MHz): δ = 1.06 (m, 4H, C*H*$_2$C*H*$_2$CHCO), 1.18 (m, 4H, C*H*$_2$C*H*$_2$CHCO), 2.24 (tt, *J* = 7.8, 4.5 Hz, 2H, C*H*COCH=), 7.05 (s, 2H, COC*H*=). - ^{13}C NMR (100 MHz): δ = 12.2 (t, *C*H$_2$*C*H$_2$CHCO), 20.4 (d, CH$_2$*C*HCO), 136.1 (d, CO*C*H=), 200.4 (s, *C*O).

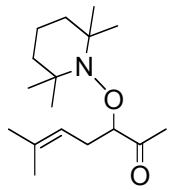
6-Methyl-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)-5-hepten-2-one 3-11j



Flash chromatography (hexane/ethyl acetate 80:1, gradient to 5:1) afforded ferrocene, followed by an inseparable mixture of **3-11j** and **3-11'j**, **3-12'** (containing small amounts of an unknown a dimer, which contains the tetramethylpiperidinyloxy unit), aldol/TEMPO trapping product **3-13j**, **3-12j** and **3-14j**. For structure elucidation and analysis, a second and third purification was performed. Yield deprotonation 5 min: **3-11j** and **3-11'j** 90 mg (16%, 1.9:1), **3-12'j** 14 mg (6%, as a 30 mg mixture with a TEMPO-containing dimer ($C_{26}H_{45}NO_2$)), **3-13j** 110 mg (26%), **3-12j** 20 mg (8%). Yield with LiCl, deprotonation 5 min: **3-11j** and **3-11'j** 244 mg (43%, 7.4:1), **3-13j** 79 mg (19%) and **3-14j** 24 mg (9%). The NMR data of compound **3-12j** are identical with those reported earlier.[25] Pale yellow oils. The following analyses were performed with the regioisomeric mixture of **3-11j** and **3-11'j**: IR (film): $\tilde{\nu}$ = 2972, 2929, 2873, 1718, 1467, 1447, 1376, 1359, 1262, 1244, 1209, 1185, 1133, 1071, 991, 972, 957, 925, 792, 733, 706 cm^{-1}. - MS (+ESI): *m/z* (%) = 585 (13) [2M+Na$^+$], 304 (100) [M+Na$^+$], 179 (11) [TEMPO+Na$^+$]. - Combustion analysis: $C_{17}H_{31}NO_2$ (281.43): calc. C 72.55, H 11.10, N 4.98; found C 72.56, H 11.25, N 5.22.

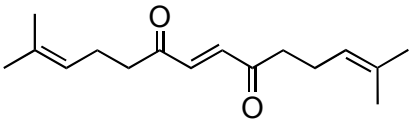
3-11j: R_f = 0.56 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 1.13 (s, 6H, NCC*H*$_3$), 1.16 (s, 6H, NCC*H*$_3$), 1.26-1.56 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.62 (s, 3H, =CC*H*$_3$), 1.67 (d, *J* = 1.1 Hz, 3H, =CC*H*$_3$), 2.28 (q, *J* = 7.3 Hz, 2H, =CHC*H*$_2$), 2.53 (t, *J* = 7.4 Hz, 2H, OCC*H*$_2$CH$_2$), 4.38 (s, 2H, C*H*$_2$ON), 5.09 (tq, *J* = 7.2, 1.4 Hz, 1H, =C*H*). - ^{13}C NMR (100 MHz): δ = 16.9 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.6 (q, =C*C*H$_3$), 20.1 (q, NC*C*H$_3$), 21.9 (t, =CH*C*H$_2$), 25.6 (q, =C*C*H$_3$), 32.8 (q, NC*C*H$_3$), 39.5 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 39.6 (t, *C*H$_2$CO), 60.0 (s, N*C*CH$_3$), 83.1 (t, *C*H$_2$ON), 122.7 (d, *C*H=C), 132.6 (s, CH=*C*), 208.4 (s, *C*O).

6-Methyl-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)-5-hepten-2-one 3-11'j



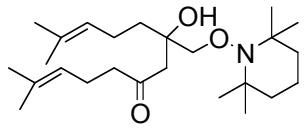
R_f = 0.56 (hexane/EtOAc 10:1). - Detectable resonances: ^{1}H NMR (400 MHz): δ = 1.13 (s, 6H, NCC*H*$_3$), 1.16 (s, 6H, NCC*H*$_3$), 1.43-1.50 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.59 (s, 3H, =CC*H*$_3$), 1.67 (s, 3H, =CC*H*$_3$), 2.17 (s, 3H, C*H*$_3$CO), 4.14 (dd, *J* = 9.5, 4.4 Hz, 1H, C*H*ON), 5.02 (tq, *J* = 7.3, 1.4 Hz, 1H, =C*H*). - ^{13}C NMR (100 MHz): δ = 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.8 (q, =C*C*H$_3$), 25.7 (q, =C*C*H$_3$), 27.0 (q, OC*C*H$_3$), 30.5 (t, =CH*C*H$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 60.0 (s, N*C*CH$_3$), 91.0 (d, *C*HON), 117.8 (d, *C*H=C), 134.5 (s, CH=*C*), 210.3 (s, *C*O).

2,13-Dimethyl-2,7,12-tetradecatriene-6,9-dione 3-12'j



Product **3-12'j** was isolated as an inseparable mixture with a dimer, which contained the tetramethylpiperidinyloxy unit ($C_{26}H_{45}NO_2$). R_f = 0.50, 0.47 (hexane/EtOAc 10:1), R_f = 0.68 (hexane/EtOAc 5:1). - Detectable resonances of **3-12'j**: ^{1}H NMR (400 MHz): δ = 1.62 (s, 6H, *C*H$_3$C=), 1.68 (d, *J* = 1.0 Hz, 6H, *C*H$_3$C=), 2.32 (q, *J* = 7.3 Hz, 4H, =CHC*H*$_2$), 3.17 (t, *J* = 7.5 Hz, 4H, C*H*$_2$CO), 5.09 (m, 2H, C*H*=CCH$_3$), 6.85 (s, 2H, COC*H*=C*H*CO). - ^{13}C NMR (100 MHz): δ = 17.6 (q, *C*H$_3$C=), 22.3 (t, *C*H$_2$CH=), 25.5 (q, *C*H$_3$C=), 41.6 (d, *C*H$_2$CO), 122.1 (d, *C*H=C), 133.1 (s, *C*=CH), 136.1 (d, CO*C*H=*C*HCO), 200.2 (s, *C*O).

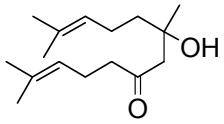
6-Hydroxy-2,12-dimethyl-6-(2,2,6,6-tetramethylpiperidin-1-yloxymethyl)-2,11-tridecadien-8-one 3-13j



R_f = 0.42 (hexane/EtOAc 10:1). - ^{1}H NMR (400 MHz): δ = 1.09 (br. s, 6H, NCC*H*$_3$), 1.14 (s, 3H, NCC*H*$_3$), 1.15 (s, 3H, NCC*H*$_3$), 1.22-1.52 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.56 (m, 2H, CH$_2$C*H*$_2$COH), 1.61 (s, 6H, 2 =CC*H*$_3$), 1.67 (s, 6H, 2 =CC*H*$_3$), 2.07 (m, 2H, C*H*$_2$CH$_2$COH), 2.26 (m, 2H, O=CCH$_2$C*H*$_2$CH=), 2.48 (m, 2H, CH$_2$C*H*$_2$C=O), 2.67 (AB system, *J* = 16.9 Hz,

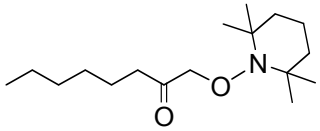
2H, O=CCH_2COH), 3.75 (AB system, J = 8.9 Hz, 2H, CH_2ON), 5.07 (m, 2H, CH=). - ^{13}C NMR (100 MHz): δ = 16.6 (t, NCCH$_2$$CH_2CH_2$CN), 17.2 (q, =C$CH_3$), 17.3 (q, =C$CH_3$), 19.9 (q, NC$CH_3$), 21.5 (t, CH$_2CH_2$COH), 21.7 (t, CH$_2CH_2$C=O), 25.2 (q, =CCH$_3$), 25.3 (q, =CCH$_3$), 32.6 (q, NCCH$_3$), 32.7 (q, NCCH$_3$), 37.8 (t, CH$_2$$CH_2$COH), 39.4 (t, NC$CH_2CH_2$$CH_2$CN), 44.1 (t, CH$_2$$CH_2$C=O), 47.0 (t, OC$CH_2$COH), 59.6 (s, N$CCH_3$), 72.9 (s, COH), 80.8 (t, CH$_2$ON), 122.1 (d, CH=C), 123.9 (d, CH=C), 131.2 (s, CH=C), 132.4 (s, CH=C), 211.9 (s, CO). - IR (film): $\tilde{\nu}$ = 3491, 2970, 2928, 1704, 1449, 1406, 1376, 1359, 1262, 1243, 1184, 1132, 1077, 1051, 991, 957, 925, 835, 814, 705 cm^{-1}. - MS (+ESI): *m/z* (%) = 707 (16), 585 (30), 563 (19), 430 (100) [M+Na$^+$], 408 [M+H$^+$], 304 (20) [(CH$_3$)$_2$C=CHCH$_2$CH$_2$COCH$_2$OTMP+Na$^+$], 301 (44). - HRMS: $C_{25}H_{46}NO_3^+$: calc. 408.3478; found 408.3472. - Combustion analysis: $C_{25}H_{45}NO_3$ (407.63): calc. C 73.66, H 11.13, N 3.44; found C 73.71, H 11.46, N 3.49.

6-Hydroxy-2,6,12-trimethyl-2,11-tridecadien-8-one 3-14j



R_f = 0.46 (hexane/EtOAc 5:1). - ^{1}H NMR (400 MHz): δ = 1.21 (s, 3H, C(OH)CH_3), 1.50 (m, 2H, CH$_2$CH_2COH), 1.608 (s, 3H, =CCH_3), 1.611 (s, 3H, =CCH_3), 1.68 (s, 6H, 2 =CCH_3), 2.03 (m, 2H, CH_2CH$_2$COH), 2.25 (m, 2H, CH_2CH$_2$C=O), 2.44 (m, 2H, CH$_2$CH_2C=O), 2.58 (AB system, J = 17.0 Hz, 2H, COCH_2COH), 3.83 (s, 1H, OH), 5.06 (m, 2H, CH=C(CH$_3$)$_2$). - ^{13}C NMR (100 MHz): δ = 17.56 (q, =CCH$_3$), 17.60 (q, =CCH$_3$), 22.1 (t, CH$_2$CH$_2$C=O), 22.6 (t, CH$_2$CH$_2$COH), 25.58 (q, =CCH$_3$), 25.61 (q, =CCH$_3$), 26.7 (q, C(OH)CH$_3$), 41.9 (t, C(OH)CH$_2$CH$_2$), 44.6 (t, CH$_2$$CH_2$C=O), 51.5 (t, CO$CH_2$COH), 71.6 (s, COH), 122.3 (d, CH=C), 124.2 (d, CH=C), 131.6 (s, CH=C), 133.0 (s, CH=C), 213.0 (s, CO).

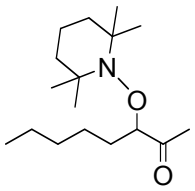
1-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-2-octanone 3-11k



Flash chromatography (hexane/ethyl acetate 80:1, gradient to 5:1) gave ferrocene, followed by a mixture of **3-11k** and **3-11'k**, a mixture of **3-11k** and **3-12'k**, aldol/TEMPO trapping product **3-13k**, and finally a mixture of **3-13k** and **3-14k**. The yield was determined from the NMR spectra. The products were further purified. Pale yellow oils. Yield with LiCl, 5 min deprotonation: **3-11k** and **3-11'k** 166 mg (29%, 12:1), **3-13k** 124.3 mg (30%). Yield with

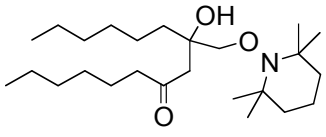
LiCl, 30 min deprotonation: **3-11k** and **3-11'k** 212 mg (37%, 8.8:1), small amounts of **3-12'k**, **3-13k** 101mg (24%) and **3-14k** 39 mg (14%). Pale yellow oils. R_f = 0.47 (hexane/EtOAc 10:1). - IR (film): $\tilde{\nu}$ = 2929, 2870, 1718, 1466, 1376, 1360, 1262, 1244, 1209, 1184, 1132, 1074, 993, 972, 957, 926, 791, 722, 705 cm^{-1}. - MS (+ESI): *m/z* (%) = 589 (10) [2M+Na^+], 306 (100) [M+Na^+], 179 (3) [TEMPO+Na^+]. - Combustion analysis: $C_{17}H_{33}NO_2$ (283.45): calc. C 72.03, H 11.73, N 4.94; found C 71.92, H 11.74, N 5.07. - ^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.13 (s, 6H, $NCCH_3$), 1.16 (s, 6H, $NCCH_3$), 1.22-1.35 (m, 7H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_3$), 1.47 (m, 4H, $NCCH_2CH_2CH_2CN$), 1.58 (m, 3H, CH_2CH_2CO, $NCCH_2CH_2CH_2CN$), 2.51 (t, *J* = 7.4 Hz, 2H, CH_2CO), 4.39 (s, 2H, CH_2ON). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH_2CH_3), 16.9 (t, $NCCH_2CH_2CH_2CN$), 20.0 (q, $NCCH_3$), 22.4 (t, CH_2CH_3), 23.1 (t, $CH_2CH_2C{=}O$), 28.8 (t, $CH_2CH_2CH_3$ or $CH_2CH_2CH_2CH_3$), 31.5 (t, $CH_2CH_2CH_3$ or $CH_2CH_2CH_2CH_3$), 32.7 (q, $NCCH_3$), 39.5 (t, $NCCH_2CH_2CH_2CN$), 39.6 (t, CH_2CH_2CO), 59.9 (s, $NCCH_3$), 83.0 (t, CH_2ON), 208.7 (s, CO).

3-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-2-octanone 3-11'k



R_f = 0.47 (hexane/EtOAc 10:1). - Detectable resonances: ^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH_2CH_3), 2.20 (s, 3H, CH_3CO), 4.09 (dd, *J* = 4.0, 9.8 Hz, 1H, CHON). - ^{13}C NMR (100 MHz): δ = 13.8 (q, CH_2CH_3), 17.0 (t, $NCCH_2CH_2CH_2CN$), 22.3 (t, CH_2CH_3), 23.9 (t, CH_2), 26.3 (q, CH_3CO), 31.3 (t, CH_2), 31.7 (t, CH_2), 40.2 (t, $NCCH_2CH_2CH_2CN$), 91.6 (d, CHON), 210.5 (s, CO).

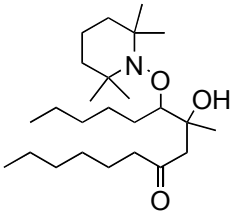
7-Hydroxy-7-(2,2,6,6-tetramethylpiperidin-1-yloxymethyl)pentadecan-9-one 3-13k



R_f = 0.37 (hexane/EtOAc 10:1). - IR (film): $\tilde{\nu}$ = 3498, 2928, 2871, 2858, 1702, 1467, 1407, 1374, 1360, 1262, 1244, 1133, 1059, 1046, 993, 956, 925, 820, 725 cm^{-1}. - ^{1}H NMR (400 MHz): δ = 0.87 (t, *J* = 6.7 Hz, 3H, CH_2CH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 1.09 (s, 6H, $NCCH_3$), 1.12 (s, 3H, $NCCH_3$), 1.14 (s, 3H, $NCCH_3$), 1.28-1.70 (m, 24H, $NCCH_2CH_2CH_2CN$, $CH_3CH_2CH_2CH_2CH_2CH_2COH$, $CH_3CH_2CH_2CH_2CH_2CH_2CO$), 2.47 (dt, *J* = 1.7, 7.4 Hz, 2H, $CH_2CH_2C{=}O$), 2.55 (A part of AB system, *J* = 16.9 Hz, 1H,

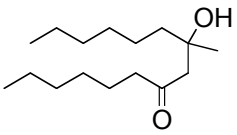
COC*H*$_2$COH), 2.75 (B part of AB system, *J* = 16.8 Hz, 1H, COC*H*$_2$COH), 3.74 (AB system, *J* = 8.8 Hz, 2H, C*H*$_2$ON), 4.03 (s, 1H, O*H*). - ^{13}C NMR (100 MHz): δ = 13.89 (q, CH$_2$*C*H$_3$), 13.94 (q, CH$_2$*C*H$_3$), 16.9 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.2 (q, NC*C*H$_3$), 22.4 (t, CH$_3$*C*H$_2$), 22.5 (t, CH$_3$*C*H$_2$), 23.1 (t, *C*H$_2$), 23.2 (t, *C*H$_2$), 28.7 (t, *C*H$_2$), 29.7 (t, *C*H$_2$), 31.5 (t, *C*H$_2$), 31.7 (t, *C*H$_2$), 33.0 (q, NC*C*H$_3$), 38.4 (t, *C*H$_2$), 39.7 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 44.5 (t, CH$_2$*C*H$_2$C=O), 47.3 (t, OC*C*H$_2$COH), 59.9 (s, N*C*CH$_3$), 73.4 (s, *C*OH), 81.2 (t, *C*H$_2$ON), 212.7 (s, *C*O). - MS (+ESI): *m/z* (%) = 434 (100) [M+Na$^+$], 412 (57) [M+H$^+$], 301 (5), 277 (6), 241 (9) [M$^+$−C$_6$H$_{13}$CO−C$_4$H$_9$]. - HRMS: C$_{25}$H$_{50}$NO$_3^+$: calc. 412.3791; found 412.3785.

7-Hydroxy-7-methyl-6-(2,2,6,6-tetramethylpiperidin-1-yloxy)pentadecan-9-one 3-13'k



R$_f$ = 0.35 (hexane/EtOAc 10:1). - Detectable resonances: ^{1}H NMR (400 MHz): δ = 3.92 (d, 1H, *J* = 10.2 Hz, O*H*), 4.19 (dd, *J* = 9.3, 4.1 Hz, 1H, C*H*ON).

7-Hydroxy-7-methyl-pentadecan-9-one 3-14k



R$_f$ = 0.34 (hexane/EtOAc 5:1). - ^{1}H NMR (400 MHz): δ = 0.88 (m, 6H, CH$_2$C*H*$_3$), 1.19 (s, 3H, C(OH)C*H*$_3$), 1.20-1.40 (m, 14H, CH$_3$(C*H*$_2$)$_4$CH$_2$COH, CH$_3$(C*H*$_2$)$_3$CH$_2$CH$_2$C=O), 1.46 (m, 2H, CH$_2$C*H*$_2$COH), 1.56 (m, 2H, C*H*$_2$CH$_2$C=O), 2.41 (t, *J* = 7.4 Hz, 2H, CH$_2$C*H*$_2$C=O), 2.57 (AB system, *J* = 16.9 Hz, 2H, COC*H*$_2$COH), 3.89 (s, 1H, O*H*). - ^{13}C NMR (100 MHz): δ = 13.8 (q, CH$_2$*C*H$_3$), 13.9 (q, CH$_2$*C*H$_3$), 22.3 (t, CH$_3$*C*H$_2$), 22.4 (t, CH$_3$*C*H$_2$), 23.3 (t, *C*H$_2$), 23.8 (t, *C*H$_2$), 26.6 (q, *C*H$_3$COH), 28.6 (t, *C*H$_2$), 29.6 (t, *C*H$_2$), 31.4 (t, *C*H$_2$), 31.6 (t, *C*H$_2$), 42.1 (t, C(OH)*C*H$_2$CH$_2$), 44.5 (t, CH$_2$*C*H$_2$C=O), 51.2 (t, CO*C*H$_2$COH), 71.6 (s, *C*OH), 213.5 (s, *C*O).

6.2. α-Hydroxy carbonyl compounds by reduction with zinc/acetic acid

General procedure I: The pure substrates **3-2b,c**, **3-5b,d** and **3-11e,f,h** (1 mmol) were heated with zinc dust (2.65 g, 40 mmol) and AcOH (6 mL, 105 mmol) in THF (2 mL) and H$_2$O (2 mL) at 50 °C until the reaction was complete (0.5-2 h). The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel.

General procedure II for α-oxygenation in one pot: To a solution of crude **3-1a**, **3-4b** and **3-10c,f,g** (2 mmol), containing ferrocene and residual LiCl, 0.25*M* in 1:1 THF/H_2O or 0.125*M* in 3:1 THF/H_2O mixture (the crude product was completely dissolved in THF; thus the presence of ferrocene and residual LiCl required sometimes more THF; then the water was added) was added 12 mL (210 mmol) glacial acetic acid and 5.2 g (80 mmol) Zn dust at 50-60 °C. The progress of the reaction was monitored by TLC (1-3.5 h). The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel.

Isolation:

Method A: For non-volatile products: The solvent was evaporated and the product was purified by flash chromatography. If the purified product still contained small amounts of acetic acid, it was dried in high vacuum, using a cooling trap. The product (preadsorbed on silica gel for general procedure II) was purified by flash chromatography with hexane/ethyl acetate.

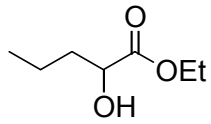
Method B: For volatile and non-volatile products: The filtrate was neutralised carefully with solid K_2CO_3 at 0 °C. The organic layer was decanted and the solid AcOK was washed well with diethyl ether. The combined organic layers were dried over Na_2SO_4. The solvent was evaporated carefully and the product was purified by flash chromatography with hexane/ethyl acetate.

Method B': The filtrate was neutralised carefully with K_2CO_3 at 0 °C and the solid AcOK was dissolved in water. The aqueous layer was extracted with diethyl ether. The combined organic layers were evaporated in vacuum. The product was purified by flash chromatography with hexane/ethyl acetate.

Method C: For water-insoluble products: The filtrate was partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether. The aqueous layer was extracted with diethyl ether. The combined ethereal layers were washed with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated in vacuum.

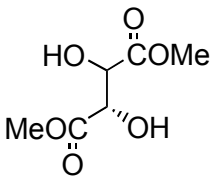
Method D: For water-soluble products: The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel with diethyl ether and ethyl acetate. The organic layer was extracted with water and $NaHCO_3$ solution. The aqueous layer was carefully neutralised with saturated $NaHCO_3$ solution, the water was evaporated and the product was extracted thoroughly with ethyl acetate from the colourless solid CH_3COONa.

Ethyl 2-hydroxyvalerate 3-15a[160]



Synthesis according to general procedure II/method A: Yield 223 mg (76%) as a colourless oil. R_f (hexane/ethyl acetate 10:1) = 0.21. - ^{1}H NMR (200 MHz): δ = 0.90 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.32-1.82 (m, 4H, $CH_2CH_2CH_3$), 2.93 (br. s, 1H, OH), 4.13 (m, 1H, CHOH), 4.20 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O). - ^{13}C NMR (50 MHz): δ = 13.6 (q, $CH_2CH_2CH_3$), 14.1 (q, OCH_2CH_3), 18.0 (t, $CH_2CH_2CH_3$), 36.4 (t, $CHCH_2CH_2$), 61.5 (t, CH_2O), 70.2 (d, CH), 175.5 (s, CO_2).

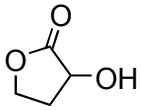
(2*S*,3*R*)- and (2*S*,3*S*)-Dimethyl 2,3-tartrates 3-15b



Synthesis according to general procedure I/method B gave a 1:2 mixture of *L*- and *meso*-**3-15b** and 2,2,6,6-tetramethylpiperidinium acetate (340 mg). The products could not be separated from the mixture. Pale yellow oils. Yield calculated from the NMR spectra: 133 mg (75%).

R_f (EtOAc) = 0.51. - (2*S*,3*R*)-**3-15b**: ^{1}H NMR (400 MHz): δ = 3.78 (s, 6H, $COOCH_3$), 4.68 (s, 2H, CHOH), 7.00-8.03 (br. s, 2H, OH). - ^{13}C NMR (100 MHz): δ = 52.3 (q, CH_3O), 73.1 (d, CHOH), 171.6 (s, CO). - (2*S*,3*S*)-**3-15b**: ^{1}H NMR (400 MHz): δ = 3.83 (s, 6H, $COOCH_3$), 4.62 (s, 2H, CHOH), 7.00-8.03 (br. s, 2H, OH). - ^{13}C NMR (100 MHz): δ = 52.6 (q, CH_3O), 72.3 (d, CHOH), 171.6 (s, CO).

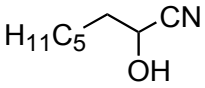
2-Hydroxybutyrolactone 3-15c[161]



Synthesis according to general procedure I/isolation method D: Yield 55 mg (54%). Pale yellow oil, soluble in water.

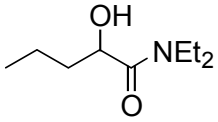
R_f(hexane/EtOAc 1:1) = 0.2. - ^{1}H NMR (200 MHz): δ = 2.22 (m, 1H, CH_2CHOH), 2.54 (m, 1H, CH_2CHOH), 3.45 (br. s, 1H, OH), 4.17 (m, 1H, CH_2OCO), 4.37 (m, 1H, CH_2OCO), 4.50 (dd, *J* = 10.1, 8.3 Hz, 1H, CHOH). - ^{13}C NMR (50 MHz): δ = 30.8 (t, CH_2CHOH), 65.4 (t, $CH_2OC{=}O$), 67.3 (d, CHOH), 178.7 (s, CO).

2-Hydroxyoctonitrile 3-16b[162]



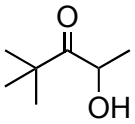
Synthesis according to general procedure I/ method C: Yield 133 mg (94%). General procedure II/method C: Yield 240 mg (85%). General procedure II/method C/15 mmol setup: Yield 1.14 g (54%) as a pale yellow oil. R_f (hexane/EtOAc 2:1) = 0.72. - IR (film): $\tilde{\nu}$ = 3448, 2955, 2928, 2859, 1459, 1417, 1379, 1337, 1125, 1069, 1039, 952, 899, 821, 725 cm^{-1}. - ^1H NMR (200 MHz): δ = 0.89 (t, *J* = 6.5 Hz, 3H, C*H*$_3$CH$_2$), 1.30-1.53 (m, 8H, CH$_3$(C*H*$_2$)$_4$), 1.84 (m, 2H, C*H*$_2$CH), 3.32 (br. s, O*H*), 4.47 (t, *J* = 6.8 Hz, 1H, C*H*OH). - ^{13}C NMR (50 MHz): δ = 13.9 (q, *C*H$_3$CH$_2$), 22.4 (t, *C*H$_3$*C*H$_2$), 24.4 (t, CH$_3$CH$_2$CH$_2$*C*H$_2$), 28.5 (t, *C*H$_2$), 31.5 (t, *C*H$_2$), 35.1 (t, *C*H$_2$), 61.2 (d, *C*HOH), 120.1 (s, *C*N).

***N,N*-Diethyl-2-hydroxy pentanoic amide 3-16d**



Synthesis according to general procedure I/method A: Yield 144 mg (83%). Pale yellow oil. R_f = 0.29 (hexane/EtOAc 2:1). - ^1H NMR (200 MHz): δ = 0.91 (t, *J* = 6.9 Hz, 3H, CH$_2$CH$_2$C*H*$_3$), 1.10 (t, *J* = 7.1 Hz, 3H, NCH$_2$C*H*$_3$), 1.18 (t, *J* = 7.2 Hz, 3H, NCH$_2$C*H*$_3$), 1.35-1.58 (m, 4H, CHC*H*$_2$C*H*$_2$CH$_3$), 3.14-3.38 (m, 3H, NC*H*$_2$), 3.53 (sext, *J* = 6.7 Hz, 1H, NC*H*$_2$), 4.27 (dd, *J* = 6.9, 3.3 Hz, 1H, C*H*OH), 5.24 (br. s, 1H, OH). - ^{13}C NMR (50 MHz): δ = 12.7 (q, CH$_2$CH$_2$*C*H$_3$), 13.8 (q, NCH$_2$*C*H$_3$), 14.0 (q, NCH$_2$*C*H$_3$), 18.2 (t, CH$_2$*C*H$_2$CH$_3$), 37.5 (t, CH*C*H$_2$), 40.2 (t, *C*H$_2$N), 40.9 (t, *C*H$_2$N), 67.7 (d, *C*HOH), 173.8 (s, *C*O). - IR (film): $\tilde{\nu}$ = 3418, 2962, 2936, 2874, 1636, 1464, 1399, 1382, 1363, 1309, 1281, 1220, 1122, 1101, 1071 cm^{-1}. - MS (EI): *m/z* (%) = 173 (1.2) [M^+], 131 (32) [M^+–C_3H_6], 130 (20) [M^+–C_3H_7], 101 (30) [M^+–C_3H_7–C_2H_5], 100 (85) [$Et_2NC{=}O^+$], 86 (47) [M^+–C_3H_7–C_2H_5–CH_3], 72 (100) [NEt_2 and M^+–NEt_2–Et], 58 (27) [M^+–C_3H_7–NEt_2], 44 (24). - Combustion analysis: $C_9H_{19}NO_2$ (173.25): calc. C 62.39, H 11.05, N 8.08; found C 62.28, H 11.38, N 7.87.

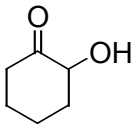
2,2-Dimethyl-4-hydroxypentan-3-one 3-17e[163]



Synthesis according to general procedure I/method B: Yield 72 mg (55%). Isolation method B': Yield 96 mg (71%). General procedure II/method B': Yield 80 mg (31%). Pale yellow oil.

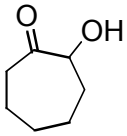
R_f (hexane/EtOAc 5:1) = 0.5. - ^{1}H NMR (200 MHz): δ = 1.14 (s, 9H, (C*H*$_3$)$_3$C), 1.28 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH), 3.20 (br. s, 1H, OH), 4.57 (q, *J* = 6.7 Hz, 1H, C*H*OH). - ^{13}C NMR (50 MHz): δ = 21.4 (q, CH*C*H$_3$), 26.6 (q, C(*C*H$_3$)$_3$), 42.6 (s, *C*(CH$_3$)$_3$), 68.4 (d, *C*HOH), 218.4 (s, *C*O).

2-Hydroxycyclohexanone 3-17f[164]



Synthesis according to general procedure I/method B: Yield 103 mg (90%). General procedure II/ method B: Yield 106 mg (46%). R_f (hexane/EtOAc 2:1) = 0.43. - ^{1}H NMR (200 MHz): δ = 1.32-2.00 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$CO), 2.08 (m, 1H, C*H*$_2$CHOH or C*H*$_2$CO), 2.16-2.59 (m, 3H, C*H*$_2$C(O)CH(OH)C*H*$_2$), 4.08 (dd, *J* = 16.7, 1.3 Hz, 1H, C*H*OH), 5.67 (br. s, 1H, O*H*). - ^{13}C NMR (50 MHz): δ = 23.3 (t, *C*H$_2$), 27.5 (t, *C*H$_2$), 36.6 (t, *C*H$_2$CHOH), 39.4 (t, *C*H$_2$CO), 75.3 (d, *C*HOH), 207.3 (s, *C*O).

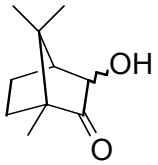
2-Hydroxy cycloheptanone 3-17g[165]



Synthesis according to general procedure II/method B/the crude product was preadsorbed on silica gel: Yield 150 mg (59%). Colourless oil.

R_f(hexane/EtOAc 2:1) = 0.5. - ^{1}H NMR (200 MHz): δ = 1.29-2.13 (m, 8H, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CHOH), 2.46 (ddd, *J* = 17.2, 10.4, 3.7 Hz, 1H, C*H*$_2$CO), 2.71 (m, 1H, C*H*$_2$CO), 3.85 (br. s, 1H, O*H*), 4.30 (dd, *J* = 9.4, 3.7 Hz, 1H, C*H*OH). - ^{13}C NMR (50 MHz): δ = 23.4 (t, *C*H$_2$), 26.5 (t, *C*H$_2$), 29.4 (t, *C*H$_2$), 33.7 (t, *C*H$_2$CHOH), 40.0 (t, *C*H$_2$C=O), 76.9 (d, *C*HOH), 213.7 (s, *C*O).

2-*exo*- and 2-*endo-(R)*-Hydroxy-camphor 3-17h[166]



Synthesis according to general procedure I/isolation method A: Yield 120 mg (71%), *2-endo:2-exo*-**3-17h** 1:1.1. Isolation method C: Yield 146 mg (87%), *2-endo:2-exo*-**3-17h** 8.5:1. Colourless solid.

2-*endo*-3-17h: R_f = 0.46 (hexane/EtOAc 2:1). - ^{1}H NMR (400 MHz): δ = 0.84 (s, 3H, C(C*H*$_3$)$_2$), 0.89 (s, 3H, C(C*H*$_3$)$_2$), 0.97 (s, 3H, CH$_2$CC*H*$_3$), 1.37 (m, 1H, CH$_2$C*H*$_2$CCH$_3$), 1.67 (m, 2H, C*H*$_2$C*H*$_2$CH), 1.94 (m, 1H, CH$_2$C*H*$_2$CH), 2.22 (t, *J* = 4.6 Hz, 1H, CH$_2$C*H*CHOH), 3.39 (br. s, 1H, OH), 4.18 (d, *J* = 5.1 Hz, 1H, C*H*OH). - ^{13}C NMR (100 MHz): δ = 8.9 (q, CH$_2$C*C*H$_3$), 17.5 (t, CH$_2$*C*H$_2$CH), 18.5 (q, CHC*C*H$_3$), 19.6 (q, CHC*C*H$_3$), 32.2 (t, C*C*H$_2$CH$_2$), 42.7 (s, *C*(CH$_3$)$_2$), 48.3 (d, *C*HCHOH), 58.1 (s, CH$_3$*C*C=O), 74.1 (d, *C*HOH), 220.5 (s, C=O). - **2-*exo*-3-17h:** R_f = 0.46 (hexane/EtOAc 2:1). - ^{1}H NMR (400 MHz): δ = 0.89 (s, 3H, CH$_2$CC*H*$_3$), 0.91 (s, 3H, C(C*H*$_3$)$_2$), 0.96 (s, 3H, C(C*H*$_3$)$_2$), 1.37 (m, 2H, C*H*$_2$C*H*$_2$CCH$_3$), 1.67 (m, 1H, C*H*$_2$CH$_2$CH), 1.94 (m, 1H, CH$_2$C*H*$_2$CH), 2.05 (d, *J* = 4.7 Hz, 1H, CH$_2$C*H*CHOH), 3.39 (br. s, 1H, OH), 3.72 (s, 1H, C*H*OH). - ^{13}C NMR (100 MHz): δ = 8.6 (q, CH$_2$C*C*H$_3$), 19.7 (q, CHC*C*H$_3$), 20.6 (q, CHC*C*H$_3$), 24.8 (t, CH$_2$*C*H$_2$CH), 28.2 (t, C*C*H$_2$CH$_2$), 46.4 (s, *C*(CH$_3$)$_2$), 49.0 (d, *C*HCHOH), 56.7 (s, CH$_3$*C*C=O), 76.9 (d, *C*HOH), 220.2 (s, C=O).

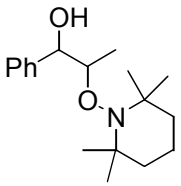
6.3. Reduction of α-(tetramethylpiperidinyloxy)carbonyl compounds with hydride reagents

β-(2,2,6,6-Tetramethylpiperidin-1-yloxy) alcohols

Method A: Excess $NaBH_4$ (46 to 68 mg, 1.2 to 1.8 equiv.) was added to a solution of 1 mmol **3-11a**, **3-11b**, **3-11f**, **3-11g**, or **3-11h** in 5 mL dry methanol at 0 °C or r.t. in one portion. The reaction was monitored by TLC. After completion 10 mL of water was added and stirred for 5 min. The mixture was diluted with 10 mL diethyl ether. The aqueous layer was extracted three times with diethyl ether. The combined ethereal layers were dried over Na_2SO_4. The solvent was removed in vacuum and the crude product was purified by flash chromatography.

Method B: Excess $LiAlH_4$ (46 to 68 mg, 1.2 to 1.8 equiv.) was added to a solution of 1 mmol **3-11a**, **3-11b**, **3-11f**, **3-11g**, or **3-11h** in 5 mL THF at –78 or at 0 °C. The solution was stirred until complete by TLC. The reaction was quenched with 5 drops of water, diluted with diethyl ether and warmed to room temperature. The mixture was filtered through a pad of silica with diethyl ether. The solvent was removed in vacuum and the crude product was purified by flash chromatography.

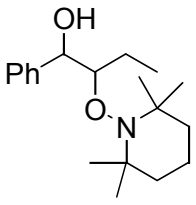
1-Phenyl-2-(2,2,6,6)-tetramethylpiperidin-1-yloxy)-1-propanol 3-20a



Flash chromatography (hexane/ethyl acetate 40:1, gradient to 10:1) gave a mixture of *syn*-**3-20a** and *anti*-**3-20a**. Colourless oil. Yield Method A (57 mg $NaBH_4$, MeOH, r.t., 25 min): 259 mg (89%) *syn/anti* 6.5:1.

R_f (hexane/EtOAc10:1) = 0.34. - IR (film): $\tilde{\nu}$ = 3100-3300 (br. w), 3070 (w), 3017 (w), 2982 (m), 2968 (m), 2931 (m), 2871 (w), 2848 (w), 1451 (m), 1380 (w), 1361 (m), 1336 (w), 1299 (w), 1258 (w), 1241 (w), 1186 (w), 1135 (s), 1057 (w), 1029 (s), 958 (w), 936 (m), 915 (w), 881 (w), 841 (w), 796 (m), 753 (s), 734 (s), 696 (s) cm^{-1}. - MS (CI) *m/z* (%): 292 (100) [M+H^+], 157 (5) [TEMPOH^+], 142 (16) [TMPH_2^+], 69 (5), 61 (8). - MS (ESI) *m/z* (%): 605 (25) [2M+Na^+], 314 (100) [M+Na^+], 180 (17) [TEMPOH+Na^+], 163 (6) [TMP+Na^+]. - HRMS (ESI): $C_{18}H_{29}NO_2Na^+$: calc. 314.2096; found 314.2107. - Combustion analysis: $C_{18}H_{29}NO_2$ (291.43): calc. C 74.18, H 10.03, N 4.81; found: C 74.15, H 10.20, N 4.70. - *syn*-isomer: ^{1}H NMR (400 MHz): δ = 0.80 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CH), 1.16 (s, 3H, NC(C*H*$_3$)$_2$), 1.19 (s, 3H, NC(C*H*$_3$)$_2$), 1.25 (br. s, 1H, O*H*), 1.32-1.65 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.40 (s, 3H, NC(C*H*$_3$)$_2$), 1.44 (s, 3H, NC(C*H*$_3$)$_2$), 4.16 (dq, *J* = 8.6, 6.3 Hz, 1H, C*H*OTMP), 4.76 (d, *J* = 8.6 Hz, 1H, C*H*OH), 7.23-7.37 (m, 5H, C*H* arom.). - ^{13}C NMR (100 MHz): δ = 16.3 (q, *C*H$_3$CH), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.4 (q, NC*C*H$_3$), 20.5 (q, NC*C*H$_3$), 32.2 (q, NC*C*H$_3$), 34.4 (q, NC*C*H$_3$), 39.9 (t, NC*C*H$_2$), 40.3 (t, NC*C*H$_2$), 60.1 (s, N*C*CH$_3$), 61.3 (s, N*C*CH$_3$), 80.8 (d, *C*HOTMP), 80.9 (d, *C*HOH), 127.4 (d, *C*H arom.), 127.6 (d, *C*H arom.), 128.1 (d, *C*H arom.), 141.8 (s, *C* arom.). - *anti*-isomer: 1.01 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CH), 1.13 (s, 3H, NC(C*H*$_3$)$_2$), 1.19 (s, 3H, NC(C*H*$_3$)$_2$), 1.40 (s, 3H, NC(C*H*$_3$)$_2$), 1.44 (s, 3H, NC(C*H*$_3$)$_2$), 1.32-1.65 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 2.43 (d, *J* = 2.6 Hz, 1H, O*H*), 4.12 (dq, *J* = 13.1, 6.5, 3.2 Hz, 1H, C*H*OTMP), 5.07 (t, *J* = 2.5 Hz, 1H, C*H*OH), 7.23-7.37 (m, 5H, C*H* arom.). - ^{13}C NMR (100 MHz): δ = 12.6 (q, *C*H$_3$CH), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.4 (q, NC*C*H$_3$), 20.5 (q, NC*C*H$_3$), 32.2 (q, NC*C*H$_3$), 34.4 (q, NC*C*H$_3$), 40.4 (NC*C*H$_2$), 60.1 (s, N*C*CH$_3$), 61.3 (s, N*C*CH$_3$), 74.8 (d, *C*HOH), 82.8 (d, *C*HOTMP), 126.0 (d, *C*H arom.), 126.9 (d, *C*H arom.), 128.0 (d, *C*H arom.), 141.1 (s, *C* arom.).

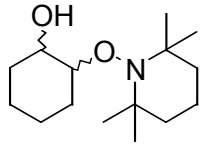
1-Phenyl-2-(2,2,6,6)-tetramethylpiperidin-1-yloxy)-butanols 3-20b



Flash chromatography (hexane/ethyl acetate 40:1, gradient to 10:1) gave a mixture of *syn*-**3-20b** and *anti*-**3-20b**. Colourless oil. Yield: Method A (1.75 equiv. $NaBH_4$, MeOH, 0 °C-r.t., 4 h): 302 mg (99%) *syn/anti* 9.2:1. Method A (46 mg $NaBH_4$, MeOH): 290 mg (95%) *syn/anti* 8:1. Method B (57 mg $LiAlH_4$, 0 °C, 35 min): 260 mg (85%) *syn/anti* 11.2:1.

R_f (hexane/EtOAc10:1) = 0.41. - IR (ATR): $\tilde{\nu}$ = 3173 (br. w), 3088 (w), 3064 (w), 2977 (m), 2930 (m), 2875 (w), 1453 (m), 1381 (m), 1339 (w), 1257 (w), 1239 (w), 1181 (w), 1131 (m), 1080 (m), 1048 (w), 1028 (w), 994 (w), 959 (s), 902 (w), 843 (w), 800 (w), 757 (s), 729 (m), 699 (s), 640 (w) cm^{-1}. - MS (CI) *m/z* (%): 306 (100) [M+H^+], 157 (5) [TEMPOH^+], 142 (20) [$TMPH_2^+$]. - MS (ESI) *m/z* (%): 633 (9) [2M+Na^+], 328 (100) [M+Na^+], 180 (9) [TEMPOH+Na^+], 148 (7) [M-TEMPOH^+]. - HRMS (ESI): $C_{19}H_{31}NO_2Na^+$: calc. 328.2252; found 328.2241. - Combustion analysis: $C_{19}H_{31}NO_2$ (305.45): calc. C 74.71, H 10.23, N 4.59; found: C 74.79, H 10.41, N 4.63. - *syn*-isomer: ^{1}H NMR (400 MHz): δ = 0.79 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.02 (m, 1H, C*H*$_2$CH$_3$), 1.07-1.23 (m+br. s, 2H, C*H*$_2$CH$_3$, O*H*), 1.10 (s, 3H, NC(C*H*$_3$)$_2$), 1.15 (s, 3H, NC(C*H*$_3$)$_2$), 1.30-1.59 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.37 (s, 3H, NC(C*H*$_3$)$_2$), 1.39 (s, 3H, NC(C*H*$_3$)$_2$), 3.94 (dt, *J* = 8.5, 3.1 Hz, 1H, C*H*OTMP), 4.80 (d, *J* = 8.8 Hz, 1H, C*H*OH), 7.15-7.31 (m, 5H, C*H* arom.). - ^{13}C NMR (100 MHz): δ = 10.1 (q, CH$_2$*C*H$_3$), 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.53 (q, NC*C*H$_3$), 20.55 (q, NC*C*H$_3$), 24.1 (t, *C*H$_2$CH$_3$), 31.8 (q, NC*C*H$_3$), 34.5 (q, NC*C*H$_3$), 39.9 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.3 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 60.2 (s, N*C*(CH$_3$)$_2$), 61.7 (s, N*C*(CH$_3$)$_2$), 79.6 (d, *C*HOH), 84.9 (d, *C*HON), 127.4 (d, *C*H arom.), 127.5 (d, *C*H arom.), 128.0 (d, *C*H arom.), 141.8 (s, *C* arom.). - *anti*-isomer, detectable resonances: ^{1}H NMR (400 MHz): δ = 0.73 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 2.44 (d, *J* = 4.4 Hz, 1H, O*H*), 3.94 (m, 1H, C*H*OTMP), 5.10 (br. s, 1H, C*H*OH), 7.15-7.31 (m, 5H, C*H* arom.). - ^{13}C NMR (100 MHz): δ = 11.3 (q, CH$_2$*C*H$_3$), 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 24.1 (t, *C*H$_2$CH$_3$), 40.7 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 60.2 (s, N*C*(CH$_3$)$_2$), 61.7 (s, N*C*(CH$_3$)$_2$), 73.3 (d, *C*HOH), 87.5 (t, *C*HOTMP), 126.3 (d, *C*H arom.), 126.8 (d, *C*H arom.), 127.8 (d, *C*H arom.), 141.4 (s, *C* arom.).

cis- and _trans_-2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)cyclohexanol 3-20f

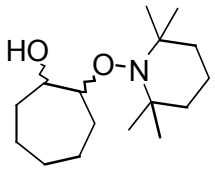


Purification by flash chromatography (hexane/ethyl acetate 20:1, gradient to 2:1) gave small amounts of *cis*-**3-20f** followed by a mixture of *cis*- and *trans*-**3-20f**. Colourless solid in the fridge, otherwise colourless oil. Yield Method A (68 mg $NaBH_4$, 0 °C, 30 min): 255 mg (100%) *cis/trans* 2.7:1. Method B (68 mg $LiAlH_4$, –78 - –60 °C, 30 min): 230 mg (90%) *trans/cis* 1.1:1. All analyses were performed on *cis/trans*-**3-20f** mixtures.

m.p. (*cis/trans* 1:1.5) 20 °C. - IR (ATR): $\tilde{\nu}$ = 3445 (w), 3265 (w), 2970 (m), 2931 (s), 2869 (m), 1451 (m), 1375 (m), 1360 (m), 1258 (w), 1240 (w), 1204 (w), 1182 (w), 1130 (s), 1068

(s), 1018 (s), 990 (m), 960 (m), 929 (w), 908 (w), 849 (w), 792 (w), 731 (w) cm^{-1}. - MS (+ESI) *m/z* (%) = 533 (7) [2M+Na^+], 278 (100) [M^++Na^+], 137 (7). - HRMS (ESI): $C_{15}H_{30}NO_2^+$: calc. 256.2277; found 256.2271. - Combustion analysis: $C_{15}H_{29}NO_2$ (255.40): calc. C 70.54, H 11.45, N 5.48; found C 70.39, H 11.57, N 5.43. - *cis*-Isomer: R_f(hexane/ethyl acetate 10:1) = 0.33. - ^{1}H NMR (400 MHz): δ = 1.15 (s+m, 13H, NC(C*H*$_3$)$_2$, C*H*$_2$CH$_2$CHOTMP), 1.28-1.42 (m, 3H, NCCH$_2$C*H*$_2$CH$_2$CN, C*H*$_2$C*H*$_2$CHOH), 1.43-1.77 (m, 8H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$CHOTMP), 1.91 (m, 2H, C*H*$_2$CH$_2$CH$_2$C*H*$_2$), 2.06 (s, 1H, O*H*), 3.65 (ddd, *J* = 11.5, 4.4, 2.7 Hz, 1H, C*H*OTMP), 4.18 (br. d, *J* = 1.9 Hz, 1H, C*H*OH). - ^{13}C-NMR (100 MHz): δ = 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.4 (t, *C*H$_2$CH$_2$CH$_2$CHOH or *C*H$_2$CH$_2$CHOH), 20.3 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 24.6 (t, *C*H$_2$CH$_2$CH$_2$CHOH or *C*H$_2$CH$_2$CHOH), 26.2 (t, *C*H$_2$CHOTMP), 31.0 (t, *C*H$_2$CHOH), 34.2 (q, NC(*C*H$_3$)$_2$), 40.4 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.9 (s, N*C*(CH$_3$)$_2$), 68.1 (d, *C*HOH), 83.5 (d, *C*HOTMP). - *trans*-Isomer: R_f(hexane/ethyl acetate 10:1) = 0.26. - ^{1}H NMR (400 MHz): δ = 1.10 (s, 3H, NC(C*H*$_3$)$_2$), 1.16 (s, 3H, NC(C*H*$_3$)$_2$), 1.08-1.25 (m, 4H, C*H*$_2$C*H*$_2$C*H*$_2$CHOH), 1.30 (s, 3H, NC(C*H*$_3$)$_2$), 1.33 (s, 3H, NC(C*H*$_3$)$_2$), 1.35 (m, 1H, NCCH$_2$C*H*$_2$CH$_2$CN), 1.43-1.77 (m, 7H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$CHOTMP), 1.83 (m, 1H, C*H*$_2$CHOTMP), 1.91 (m, 1H, C*H*$_2$CHOH), 3.76 (m, 2H, C*H*(OH)C*H*OTMP). - ^{13}C-NMR (100 MHz): δ = 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.3 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 23.7 (t, *C*H$_2$CH$_2$CH$_2$CHOH or *C*H$_2$CH$_2$CHOH), 24.5 (t, *C*H$_2$CH$_2$CH$_2$CHOH or *C*H$_2$CH$_2$CHOH), 29.3 (t, *C*H$_2$CHOTMP), 32.4 (q, NC(*C*H$_3$)$_2$), 33.0 (t, *C*H$_2$CHOH), 34.5 (q, NC(*C*H$_3$)$_2$), 39.9 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.3 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 59.9 (s, N*C*(CH$_3$)$_2$), 61.3 (s, N*C*(CH$_3$)$_2$), 75.5 (d, *C*HOH), 83.8 (d, *C*HOTMP).

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)cycloheptanol 3-20g

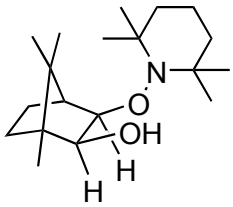


Purification by flash chromatography (hexane/ethyl acetate 40:1, gradient to 2:1) gave *cis*-**3-20g** followed by a mixture of *cis*- and *trans*-**3-20g** as colourless oils. Yield: Method A (68 mg $NaBH_4$, 0 °C, 35 min, then r.t. 20 min): 202 mg (75%) *cis/trans* 4:1; Method B (68 mg $LiAlH_4$, THF, −78 - −60 °C, 40 min) 248 mg (92%) *cis/trans* 2.9:1. All analyses were performed on *cis/trans* mixtures.

IR (film): $\tilde{\nu}$ = 3588 (w), 3491 (w), 2926 (s), 2866 (m), 1458 (m), 1376 (m), 1360 (m), 1257 (m), 1206 (w), 1182 (w), 1132 (m), 1074 (m), 1046 (w), 1007 (m), 984 (m), 957 (m), 924 (m),

794 (w) cm^{-1}. - MS (+CI) *m/z* (%): = 270 (100) [$M+H^+$], 157 (7) [$TEMPOH^+$], 142 (32) [$TMPH_2^+$], 140 (5) [TMP^+]. - Combustion analysis: $C_{16}H_{31}NO_2$ (269.42): calc. C 71.33, H 11.60, N 5.20; found C 71.33, H 11.82, N 5.42. - *cis*-Isomer: R_f(hexane/EtOAc 10:1) = 0.35. - ^{1}H NMR (200 MHz): δ = 1.14 (s, 12H, NC(C*H*$_3$)$_2$), 1.20-1.84 (m, 15H, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CHOH, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 2.00 (m, 1H, C*H*$_2$CHOH), 2.50 (s, 1H, O*H*), 3.72 (ddd, *J* = 10.3, 3.2, 2.4 Hz, 1H, C*H*OTMP), 4.23 (m, 1H, C*H*OH). - ^{13}C NMR (50 MHz): δ = 16.5 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.9 (t+q, *C*H$_2$, NC(*C*H$_3$)$_2$), 23.8 (t, *C*H$_2$), 24.9 (t, *C*H$_2$), 27.6 (t, *C*H$_2$CHOTMP), 30.9 (t, *C*H$_2$CHOH), 33.2 (q, NC(*C*H$_3$)$_2$), 39.8 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.3 (s, N*C*(CH$_3$)$_2$), 69.6 (d, *C*HOH), 86.0 (d, *C*HOTMP). - *trans*-Isomer: R_f(hexane/EtOAc 10:1) = 0.29. - ^{1}H NMR (200 MHz): δ = 1.11 (s, 3H, NCC*H*$_3$), 1.16 (s, 3H, NCC*H*$_3$), 1.28 (s, 3H, NCC*H*$_3$), 1.32 (s, 3H, NCC*H*$_3$), 1.37-1.83 (m, 16H, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CHOH, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 3.92 (m, 2H, C*H*OTMP, C*H*OH), 6.56 (s, 1H, CHO*H*). - ^{13}C NMR (50 MHz): δ = 16.5 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.8 (q, NC(*C*H$_3$)$_2$), 21.9 (t, *C*H$_2$), 22.0 (t, *C*H$_2$), 26.9 (t, *C*H$_2$), 28.5 (t, *C*H$_2$CHOTMP), 31.8 (t, *C*H$_2$CHOH), 31.9 (q, NC(*C*H$_3$)$_2$), 33.8 (q, NC(*C*H$_3$)$_2$), 39.3 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 39.6 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 59.2 (s, N*C*(CH$_3$)$_2$), 60.6 (s, N*C*(CH$_3$)$_2$), 77.0 (d, *C*HOH), 86.2 (d, *C*HOTMP).

***(1R,2S,3R)*-1,7,7-Trimethyl-3-(2,2,6,6-tetramethylpiperidin-1yloxy)bicyclo[2.2.1]heptan-2-ol 3-20h**

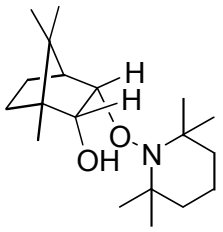


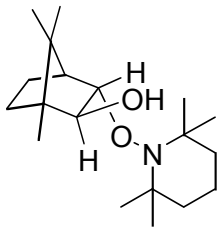
Flash chromatography (hexane/ethyl acetate 20:1, gradient to 10:1) gave *2-exo,3-exo*-**3-20h** containing small amounts of *2-endo,3-endo*-**3-20h**. Colourless solid. Yield Method B (46 mg $LiAlH_4$, 0 °C, 30 min, then 23 mg $LiAlH_4$, r.t., 30 min): 282 mg (91%) *2-exo,3-exo/2-endo,3-endo* 4.3:1. Method B (68 mg $LiAlH_4$, 0 °C, 1 h): 232 mg (75%) *2-exo,3-exo/2-endo,3-endo* 20:1. The analyses were performed on a mixture 2-*exo*,3-*exo*/2-*endo*,3-*endo*-**3-20h** 4.3:1.

R_f (hexane/EtOAc 20:1) = 0.31. - m.p. (2-*exo*,3-*exo*:2-*endo*,3-*endo* 4.3:1) 23 °C. - IR (film): $\tilde{\nu}$ = 3465 (w), 2969 (m), 2948 (s), 2931 (s), 2869 (m), 1475 (m), 1372 (m), 1361 (m), 1285 (w), 1260 (w), 1242 (w), 1184 (w), 1130 (s), 1093 (m), 1042 (s), 991 (w), 956 (m), 929 (m), 875 (w), 839 (w), 808 (m), 786 (w), 698 (w) cm^{-1}. - 2-*exo*,3-*exo*-**3-20h**: ^{1}H NMR (400 MHz): δ = 0.72 (s, 3H, C(C*H*$_3$)$_2$), 0.81 (m, 2H, C*H*$_2$C*H*$_2$CCH$_3$), 0.87 (s, 3H, CH$_2$CC*H*$_3$), 1.00 (s, 3H,

C(C*H*$_3$)$_2$), 1.13 (m, 12H, NC(C*H*$_3$)$_2$), 1.32 (m, 1H, C*H*$_2$CCH$_3$), 1.41 (br. s, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.56 (m, 1H, CH$_2$C*H*$_2$CH), 2.14 (d, *J* = 5.1 Hz, 1H, C*H*CH$_2$), 3.12 (d, *J* = 3.9 Hz, 1H, OH), 3.58 (dd, *J* = 7.4, 3.7 Hz, 1H, C*H*OH), 3.92 (d, *J* = 7.4 Hz, 1H, C*H*OTMP). - ^{13}C NMR (100 MHz): δ = 10.8 (q, *C*H$_3$CCHOH), 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.8 (q, CHC(*C*H$_3$)$_2$), 21.4 (q, CHC(*C*H$_3$)$_2$), 21.7 (q, NC*C*H$_3$), 22.3 (q, NC*C*H$_3$), 24.3 (t, CH$_2$*C*H$_2$CH), 32.6 (t, C*C*H$_2$CH$_2$), 35.0 (q, NC*C*H$_3$), 35.4 (q, NC*C*H$_3$), 40.4 (t, NC*C*H$_2$), 46.3 (s, *C*), 48.68 (s, *C*), 48.70 (d, CH$_2$*C*HCH), 59.8 (s, N*C*CH$_3$), 60.5 (s, N*C*CH$_3$), 79.9 (d, *C*HOH), 90.8 (d, *C*HOTMP). - MS (ESI) *m/z* (%): 641 (7) [2M+Na$^+$], 332 (100) [M+Na$^+$], 278 (14), 191 (18). - HRMS (ESI): $C_{19}H_{36}NO_2^+$: calc. 310.2746; found 310.2741. - Combustion analysis: $C_{19}H_{35}NO_2$ (309.49): calc. C 73.74, H 11.40, N 4.53; found: C 73.94, H 11.45, N 4.44.

***(1R,2R,3S)*-1,7,7-Trimethyl-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)bicyclo[2.2.1]heptan-2-ol 2-*endo*,3-*endo*-3-20h and *(1R,2S,3S)*-1,7,7-Trimethyl-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)bicyclo[2.2.1]heptan-2-ol 2-*exo*,3-*endo*-3-20h**



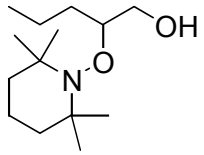


Flash chromatography (hexane/ethyl acetate 50:1, gradient to 5:1) gave 255 mg of *2-endo,3-endo*-**3-20h**, followed by 55 mg of *2-exo,3-endo*-**3-20h**, as a colourless solid. Yield Method B (68 mg LiAlH$_4$, 0 °C, 35 min, then r.t., 25 min): 310 mg (100%) *cis/trans* 4.6:1.

2-*endo*,3-*endo*-3-20h (major): R$_f$ (hexane/EtOAc10:1) = 0.68. - m.p. 121-123 °C. - ^{1}H NMR (400 MHz): δ = 0.76 (s, 3H, C(C*H*$_3$)$_2$), 0.79 (s, 3H, CH$_2$CC*H*$_3$), 0.81 (s, 3H, C(C*H*$_3$)$_2$), 0.96-1.59 (m, 20H, CHC*H*$_2$C*H*$_2$CCH$_3$, NC(C*H*$_3$)$_2$, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.64 (ddd, *J* = 12.5, 9.6, 4.5 Hz, 1H, C*H*$_2$C(CH$_3$)CHOH or CH$_2$C*H*$_2$CH), 1.76 (m, 1H, C*H*$_2$C(CH$_3$)CHOH or CH$_2$C*H*$_2$CH), 1.97 (t, *J* = 4.5 Hz, 1H, CH$_2$C*H*CHOTMP), 2.84 (d, *J* = 5.0 Hz, 1H, OH), 3.77 (ddd, *J* = 9.3, 5.0, 1.8 Hz, 1H, C*H*OH), 4.20 (ddd, *J* = 9.4, 4.4, 2.0 Hz, C*H*OTMP). - ^{13}C NMR (100 MHz): δ = 14.1 (q, *C*H$_3$CCHOH), 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.3 (q, CHC(*C*H$_3$)$_2$), 18.4 (t, CH$_2$*C*H$_2$CH), 19.7 (q, CHC(*C*H$_3$)$_2$), 20.5 (q, NC*C*H$_3$), 25.8 (t, C*C*H$_2$CH$_2$), 32.0 (q, NC*C*H$_3$), 34.0 (q, NC*C*H$_3$), 40.5 (t, NC*C*H$_2$), 43.6 (s, *C*), 49.3 (d, CH$_2$*C*HCH), 49.4 (s, *C*), 59.4 (s, N*C*CH$_3$), 60.0 (s, N*C*CH$_3$), 73.7 (d, *C*HOH), 82.9 (d, *C*HOTMP). - IR (ATR): $\tilde{\nu}$ = 3483 (w), 2991 (w), 2948 (s), 2920 (s), 2871 (m), 1463 (m), 1372 (m), 1357 (w), 1259 (w), 1185 (w), 1132 (m), 1098 (w), 1054 (s), 1024 (m), 990 (m),

951 (m), 925 (m), 876 (w), 832 (w), 807 (m), 783 (w), 719 (w) cm^{-1}. - MS (ESI) *m/z* (%): 310 (100) [M+H^+], 288 (7). - HRMS (ESI): $C_{19}H_{36}NO_2^+$: calc. 310.2746; found 310.2741. - **2-*exo*,3-*endo*-3-20h** (minor): - ^{1}H NMR (400 MHz): δ = 0.81 (s, 3H, C(C*H*$_3$)$_2$), 0.84 (s, 3H, C(C*H*$_3$)$_2$), 1.00 (q, *C*H$_3$CCHOH), 1.14 (m, 10H, NC(C*H*$_3$)$_2$, C*H*$_2$C(CH$_3$)CHOH), 1.32 (br. s, 5H, NCC*H*$_3$, NCCH$_2$C*H*$_2$CH$_2$CN), 1.43-1.52 (m, 5H, NCC*H*$_2$CH$_2$C*H*$_2$CN, CH$_2$C*H*$_2$CH), 1.56 (dt, *J* = 12.1, 4.4 Hz, 1H, C*H*$_2$CCH$_3$CHOH), 1.70 (s, 1H, O*H*), 1.80 (ddd, *J* = 12.5, 9.7, 4.4 Hz, 1H, CH$_2$C*H*$_2$CH), 2.06 (t, *J* = 4.3 Hz, 1H, CH$_2$C*H*CHON), 3.54 (d, *J* = 2.4 Hz, 1H, C*H*OH), 4.28 (dt, *J* = 4.5, 2.3 Hz, C*H*OTMP). - ^{13}C NMR (100 MHz): δ = 11.3 (q, *C*H$_3$CCHOH), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.7 (t, CH$_2$*C*H$_2$CH), 19.9 (q, CHC*C*H$_3$), 20.3 (q, NC*C*H$_3$), 20.5 (q, CHC*C*H$_3$+NC*C*H$_3$), 33.8 (q, NC*C*H$_3$), 34.0 (q, NC*C*H$_3$), 34.5 (t, C*C*H$_2$CH$_2$), 40.1 (t, NC*C*H$_2$), 46.5 (s, *C*), 49.5 (s, *C*), 49.7 (d, CH$_2$*C*HCH), 59.3 (s, N*C*CH$_3$), 59.9 (s, N*C*CH$_3$), 86.2 (d, *C*HOH), 94.8 (d, *C*HOTMP). - IR (ATR): $\tilde{\nu}$ = 3479 (w), 2922 (s), 2873 (m), 1473 (m), 1372 (m), 1358 (w), 1260 (w), 1186 (w), 1133 (m), 1099 (w), 1055 (s), 1024 (m), 991 (m), 953 (m), 926 (m), 877 (w), 833 (w), 809 (w), 784 (w), 720 (w), 673 (w) cm^{-1}. - MS (ESI) *m/z* (%): 310 (100) [M+H^+], 288 (5). - HRMS (ESI): $C_{19}H_{36}NO_2^+$: calc. 310.2746; found 310.2741.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-1-pentanol 3-23



$LiAlH_4$ (25 mg, 0.66 mmol) was added at 0 °C in one portion to a solution of **3-2a** (150 mg, 0.63 mmol) in dry THF (5 mL). After the vigorous reaction had ceased, the reaction mixture was stirred for 75 min (complete by TLC). The mixture was hydrolysed with 5 drops of water, stirred for 15 min, diluted with 15 mL diethyl ether and filtered through a pad of silica gel to remove inorganic material. The solvent was evaporated *in vacuo* and the pale yellow oil was purified by flash chromatography (hexane/EtOAc 10:1) to give **3-23** as a colourless oil.

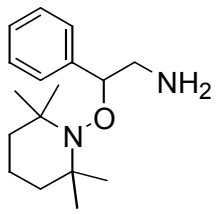
Yield 116 mg (90%). R_f = 0.18 (hexane/EtOAc 10:1); R_f = 0.5 (hexane/EtOAc 5:1). - IR (film): $\tilde{\nu}$ = 3430, 3305, 2956, 2932, 2872, 1455, 1380, 1363, 1254, 1243, 1212, 1182, 1131, 1078, 1048, 1020, 992, 976, 958, 922, 724, 653 cm^{-1}. - ^{1}H NMR (400 MHz): δ = 0.86 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.03 (s, 3H, C*H*$_3$CN), 1.10 (s, 3H, C*H*$_3$CN), 1.16 (m, 1H, NCCH$_2$C*H*$_2$CH$_2$CN), 1.25 (s, 6H, NCC*H*$_3$), 1.27-1.56 (m, 9H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH(C*H*$_2$)$_2$CH$_3$), 3.50 (br. d, *J* = 11.8 Hz, 1H, CHC*H*$_2$OH), 3.89 (dd, *J* = 11.4, 9.7 Hz, 1H, CHC*H*$_2$OH), 4.20 (dddd, *J* = 11.8, 9.4, 4.8, 2.0 Hz, 1H, C*H*ON), 5.90 (s, 1H, OH). - ^{13}C NMR

(100 MHz): δ = 14.2 (q, CH_2CH_3), 17.1 (t, $NCCH_2CH_2CH_2CN$), 19.1 (t, CH_2CH_3), 20.3 (q, $NCCH_3$), 20.4 (q, $NCCH_3$), 32.3 (q, $NCCH_3$), 33.3 (t, $CH_2CH_2CH_3$), 34.6 (q, $NCCH_3$), 39.8 (t, $NCCH_2CH_2CH_2CN$), 40.3 (t, $NCCH_2CH_2CH_2CN$), 59.7 (s, $NCCH_3$), 61.4 (s, $NCCH_3$), 68.6 (t, $CHCH_2OH$), 79.8 (d, CH_2CHCH_2OH). - MS (+ESI): *m/z* (%) = 244 (100) [M^+]. - HRMS: $C_{14}H_{30}NO_2^+$: calc. 244.2277; found 244.2271. - Combustion analysis: $C_{14}H_{29}NO_2$ (243.39): calc. C 69.09, H 12.01, N 5.75; found C 69.11, H 12.12, N 5.93.

Reduction of the nitrile function in 3-5a,b to amino alkoxyamines 3-24 and 3-25:

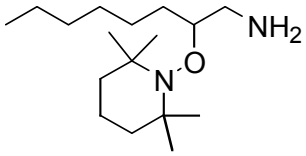
A solution of **3-5a,b** (1 mmol) dissolved in dry diethyl ether (1 mL) was added to a suspension of $LiAlH_4$ (76 mg, 2 mmol) in dry diethyl ether (2 mL) at room temperature. After 1.5 h the reaction was quenched with water (0.3 mL), diluted with diethyl ether (10 mL) and stirred for further 10 min. The reaction mixture was decanted from the soft colourless solid thus formed. The solid residue was washed 3 times with diethyl ether. The combined ethereal layers were washed twice with saturated $NaHCO_3$ solution and extracted three times with 2*N* HCl solution (10 mL). The combined aqueous layers were washed once with diethyl ether, made basic with 2*N* NaOH solution (40 mL) and extracted three times with diethyl ether (10 mL). The combined ethereal layers were washed twice with water, twice with brine, dried over Na_2SO_4, evaporated and dried in vacuum to give the pure products **3-24** and **3-25**.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-2-phenylethylamine 3-24



Yield 204 mg (74%) as a pale yellow oil. R_f = base line (hexane/EtOAc 5:1). - IR (film): $\tilde{\nu}$ = 3380, 3001, 2970, 2929, 2870, 1600, 1452, 1376, 1360, 1258, 1241, 1132, 1015, 987, 956, 922, 878, 847, 796, 759, 700 cm^{-1}. - ^1H NMR (200 MHz): δ = 0.71 (s, 3H, $NCCH_3$), 1.06-1.47 (m, 17H, $NCCH_3$, $NCCH_2CH_2CH_2CN$, NH_2), 3.11 (d, *J* = 5.5 Hz, 2H, CH_2NH_2), 4.69 (t, *J* = 5.4 Hz, 1H, CHON), 7.19-7.40 (m, 5H, Ph). - ^{13}C NMR (50 MHz): δ = 17.1 (t, $NCCH_2CH_2CH_2CN$), 20.4 (q, $NCCH_3$), 33.9 (q, $NCCH_3$), 40.4 (t, $NCCH_2CH_2CH_2CN$), 46.6 (t, CH_2NH_2), 59.8 (s, $NCCH_3$), 87.9 (d, CHON), 127.2 (d, Ph), 127.4 (d, Ph), 128.0 (d, Ph), 141.8 (s, Ph). - MS (+ESI): *m/z* (%) = 299 (18) [$M+Na^+$], 277 (100) [$M+H^+$]. - Combustion analysis: $C_{17}H_{36}N_2O$ (276.42): calc. C 73.87, H 10.21, N 10.13; found C 73.90, H 10.27, N 10.36.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-1-octylamine 3-25



Yield 260 mg (91%) as a pale yellow oil. R_f = base line (hexane/EtOAc 5:1). - IR (film): $\tilde{\nu}$ = 3380, 2926, 2857, 1577, 1464, 1376, 1360, 1297, 1258, 1241, 1208, 1182, 1132, 958, 926, 815, 786, 717 cm^{-1}. - ^1H NMR (200 MHz): δ = 0.89 (t, *J* = 6.5 Hz, 3H, CH_2CH_3), 1.13 (s, 6H, $NCCH_3$), 1.13-1.46 (m, 17H, $NCCH_2CH_2CH_2CN$, NH_2, $CH_3(CH_2)_4$, CH_2CHON), 1.29 (s, 3H, $NCCH_3$), 1.46 (s, 3H, $NCCH_3$), 1.70 (m, 1H, CH_2CHON), 2.82 (m, 2H, CH_2NH_2), 3.76 (m, 1H, CHON). - ^{13}C NMR (50 MHz): δ = 14.0 (q, CH_2CH_3), 17.2 (t, $NCCH_2CH_2CH_2CN$), 20.4 (q, $NCCH_3$), 22.6 (t, CH_3CH_2), 26.0 (t, CH_2), 29.6 (t, CH_2), 31.1 (t, CH_2), 31.8 (t, CH_2), 34.3 (q, $NCCH_3$), 40.3 (t, $NCCH_2CH_2CH_2CN$), 44.8 (t, CH_2NH_2), 59.8 (s, $NCCH_3$), 83.2 (d, CHON). - MS (+ESI): *m/z* (%) = 285 (100) $[M+H^+]$. - Combustion analysis: $C_{17}H_{36}N_2O$ (284.48): calc. C 71.77, H 12.76, N 9.85; found C 72.07, H 12.93, N 10.25.

6.4. Reactivity of α,β-unsaturated carbonyl compounds 3-28a,b towards LDA, 1-2 and 1-3

Oxygenation of methyl *trans*-2-pentenoate 3-28a in the absence of additives

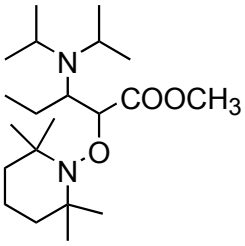
BuLi (1.625 mL, 1.6*M* in hexane, 2.6 mmol) was added to a solution of dry iPr_2NH (0.366 mL, 2.6 mmol) in 20 mL dry THF (0.1*M* substrate concentration) at –78 °C. After stirring at –78 °C for 30 min, **3-28a** (228 mg, 2 mmol) dissolved in 1 mL THF was added at –78 °C. The mixture was stirred at –78 °C for 0.5 h, then TEMPO (343 mg, 2.2 mmol) was added and the mixture was stirred for 5 min until it dissolved. Ferrocenium hexafluorophosphate was added in portions at –78 °C, as it was consumed until the reaction mixture remained blue for 20 min (total 890 mg, 2.7 mmol). Consumption of the substrate and formation of products was monitored by TLC with hexane/EtOAc 10:1. The reaction was quenched with 10 drops of water, diluted with diethyl ether and warmed to r.t.. The mixture was filtered through a pad of silica gel, which was washed with diethyl ether. The solution was concentrated in vacuo and preadsorbed on silica gel. Flash chromatography (hexane/EtOAc 80:1 gradient to 5:1) afforded a mixture of ferrocene and *anti*-**3-29a**, followed by a mixture of *anti*-**3-29a** and *syn*-**3-29a**, and finally a mixture of *anti*-**3-29a,** *syn*-**3-29a**, and **3-30a**. All analyses were performed on a mixture of *syn*-**3-29a** and *anti*-**3-29a**. A second purification afforded pure *anti*-**3-29a** and its structure was assigned by X-ray crystallography. Product **3-30a** was not

separable from the mixture. The yield was calculated from the NMR spectra: **3-29a** 33%, *anti*-**3-29a**:*syn*-**3-29a** 5.1:1; **3-30a** 10%.

Oxygenation of methyl *trans*-2-pentenoate 3-28a in the presence of HMPA

The reaction was performed as before, but 2.2 mL (13.8 mmol) of dry HMPA was added before oxidation. Flash chromatography with hexane/EtOAc 80:1 gradient to 5:1 afforded 80 mg of a complex mixture, which was not assigned.

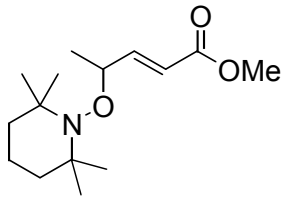
Methyl 3-(*N,N*-diisopropylamino)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)pentanoate 3-29a



IR (ATR): $\tilde{\nu}$ = 2976 (m), 2954 (m), 2934 (m), 2871 (m), 1744 (s), 1463 (w), 1393 (w), 1361 (m), 1247 (w), 1205 (s), 1175 (s), 1132 (m), 1116 (w), 1047 (s), 995 (w), 965 (m), 907 (w), 890 (w), 790 (w), 758 (w), 720 (w), 704 (m) cm^{-1}. - MS (ESI): *m/z* (%): 763 (6) [2M+Na^+], 393 (100) [M+Na^+], 142 (35) [$TMPH_2^+$]. - HRMS (ESI): $C_{21}H_{42}N_2O_3Na^+$: calc. 393.3093; found 393.3096. - Combustion analysis: $C_{21}H_{42}N_2O_3$ (370.57): calc. C 68.06, H 11.42, N 7.56; found C 68.04, H 11.69, N 7.58. - *anti*-**3-29a**: R_f(hexane/EtOAc 20:1) = 0.41. - m.p. 61-63 °C. - ^{1}H NMR (400 MHz): δ = 0.91 (d, *J* = 6.7 Hz, 6H, NCH(C*H*$_3$)$_2$), 1.05 (d, *J* = 6.6 Hz, 6H, NCH(C*H*$_3$)$_2$), 1.02-1.14 (m, 6H, NC(C*H*$_3$)$_2$), 1.10 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.18 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.26-1.56 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.41 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.62 (m, 1H, C*H*$_2$CHNCH), 1.89 (sept, *J* = 7.2 Hz, 1H, C*H*$_2$CHNCH), 3.07 (m, 3H, N(C*H*(CH$_3$)$_2$)$_2$, C*H*CHOTMP), 3.62 (s, 3H, COOC*H*$_3$), 4.42 (d, *J* = 10.0 Hz, 1H, C*H*OTMP). - ^{13}C NMR (100 MHz): δ = 13.2 (q, *C*H$_3$CH$_2$), 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.5 (q, NC(*C*H$_3$)$_2$), 20.8 (q, NC(*C*H$_3$)$_2$), 21.8 (q, NCH(*C*H$_3$)$_2$), 24.1 (q, NCH(*C*H$_3$)$_2$), 25.1 (t, CH$_3$*C*H$_2$), 33.0 (q, NC(*C*H$_3$)$_2$), 34.8 (q, NC(*C*H$_3$)$_2$), 40.6 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.9 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 46.0 (d, N*C*H(CH$_3$)$_2$), 50.7 (q, O*C*H$_3$), 59.2 (d, N*C*HCH$_2$), 59.4 (s, N*C*(CH$_3$)$_2$), 61.0 (s, N*C*(CH$_3$)$_2$), 86.7 (d, *C*HOTMP), 173.4 (s, C=O). - *syn*-**3-29a**: R_f(hexane/EtOAc 20:1) = 0.41. - ^{1}H NMR (400 MHz): δ = 0.97 (d, *J* = 6.5 Hz, 6H, NCH(C*H*$_3$)$_2$), 1.01 (d, *J* = 7.1 Hz, 6H, NCH(C*H*$_3$)$_2$), 1.02 (m, 3H, CH$_2$C*H*$_3$), 1.02-1.21 (m, 9H, NC(C*H*$_3$)$_2$), 1.26-1.56 (m, 9H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, NC(C*H*$_3$)$_2$), 1.62 (m, 1H, C*H*$_2$CHNCH), 1.98 (ddq, *J* = 3.7, 7.6, 14.5 Hz,

1H, C*H*$_2$CHNCH), 3.07 (m, 2H, N(C*H*(CH$_3$)$_2$)$_2$), 3.26 (ddd, *J* = 9.0, 5.1, 3.8 Hz, 1H, C*H*CHOTMP), 3.65 (s, 3H, COOC*H*$_3$), 4.19 (d, *J* = 5.2, 1H, C*H*OTMP). - ^{13}C NMR (100 MHz): δ = 13.3 (q, *C*H$_3$CH$_2$), 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.3 (q, NC(*C*H$_3$)$_2$), 20.5 (q, NC(*C*H$_3$)$_2$), 22.4 (q, NCH(*C*H$_3$)$_2$), 23.8 (q, NCH(*C*H$_3$)$_2$), 31.5 (t, CH$_3$*C*H$_2$), 33.0 (q, NC(*C*H$_3$)$_2$), 34.8 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.6 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 44.7 (d, N*C*H(CH$_3$)$_2$), 50.6 (q, O*C*H$_3$), 58.2 (d, N*C*HCH$_2$), 59.4 (s, N*C*(CH$_3$)$_2$), 61.0 (s, N*C*(CH$_3$)$_2$), 88.1 (d, *C*HOTMP), 173.7 (s, C=O).

Methyl 4-(2,2,6,6-tetramethylpiperidin-1-yloxy)-2-pentenoate 3-30a



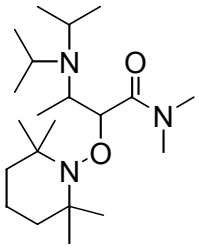
R$_f$(hexane/EtOAc 10:1) = 0.44. - ^{1}H NMR (400 MHz): δ = 1.07 (s, 3H, NC(C*H*$_3$)$_2$), 1.10 (s, 6H, NC(C*H*$_3$)$_2$), 1.16 (s, 3H, NC(C*H*$_3$)$_2$), 1.28 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.21-1.56 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 3.74 (s, 3H, COOC*H*$_3$), 4.44 (quint, *J* = 6.6 Hz, C*H*OTMP), 5.91 (d, *J* = 15.7 Hz, =C*H*COOMe), 6.98 (dd, *J* = 15.8, 6.9 Hz, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 16.4 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 19.4 (q, *C*H$_3$CH), 19.6 (q, NC(*C*H$_3$)$_2$), 33.4 (q, NC(*C*H$_3$)$_2$), 33.7 (q, NC(*C*H$_3$)$_2$), 39.4 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 50.7 (q, O*C*H$_3$), 59.0 (s, N*C*(CH$_3$)$_2$), 78.4 (d, *C*HOTMP), 118.6 (d, =*C*HCOOMe), 150.6 (d, =*C*HCHOTMP), 166.2 (s, C=O).

Oxygenation of *N,N*-dimethylcrotonamide 3-28b

To a solution of 0.183 mL (1.3 mmol) dry *i*Pr$_2$NH in 10 mL dry THF (0.1*M* substrate solution) was added 0.812 mL (1.3 mmol) of a 1.6*M* solution of BuLi in hexane dropwise via syringe at –78 °C. This solution was stirred at –78 °C for 0.5 h. A solution of 113 mg (1 mmol) of substrate dissolved in 1 mL THF was added at –78 °C. The mixture was stirred at –78 °C for 0.5 h. TEMPO (172 mg, 1.1 mmol) was added and the mixture was stirred for 5 min until it dissolved. Ferrocenium hexafluorophosphate was added in portions at –78 °C as it was consumed until the reaction mixture remained blue for 20 min. Consumption of substrate and formation of products was monitored by TLC with hexane/EtOAc 10:1. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The mixture was filtered through a pad of silica gel, which was washed with diethyl ether. The solution was concentrated in vacuo and preadsorbed on silica gel. Flash chromatography with hexane/EtOAc 80:1, gradient to 1:1 afforded ferrocene, followed by *anti*-**3-29b**, a mixture of

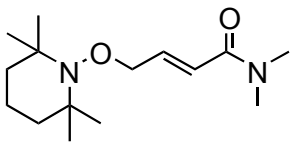
anti-**3-29b** and *syn*-**3-29b**, and finally impure **3-30b**. Analyses were performed on the mixture of *anti*-**3-29b** and *syn*-**3-29b**. Yield 200 mg (54%) of *anti*-**3-29b**:*syn*-**3-29b** 36:1, as a waxy colourless solid; 15 mg (max 5%) of **3-30b** as a pale yellow oil.

3-(*N,N*-Diisopropylamino)-*N',N'*-dimethyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-butanoic amide 3-29b



IR (ATR): $\tilde{\nu}$ = 2975 (m), 2961 (m), 2933 (s), 2872 (w), 1640 (s), 1465 (m), 1418 (w), 1393 (m), 1361 (m), 1334 (w), 1259 (w), 1240 (w), 1210 (m), 1196 (m), 1159 (w), 1133 (s), 1034 (s), 998 (w), 975 (m), 956 (m), 902 (w), 876 (w), 845 (w), 787 (w), 709 (m) cm^{-1}. - MS (ESI): *m/z* (%): 392 (9) [M+Na^+], 370 (100) [M+H^+]. - HRMS: $C_{21}H_{44}N_3O_2^+$: calc. 370.3434; found 370.3428. - *anti*-**3-29b**: ^{1}H NMR (400 MHz): δ = 0.92 (d, *J* = 6.8 Hz, 6H, NCH(C*H*$_3$)$_2$), 0.97 (s, 3H, NC(C*H*$_3$)$_2$), 1.05 (d, *J* = 6.5 Hz, 6H, NCH(C*H*$_3$)$_2$), 1.07 (s, 3H, NC(C*H*$_3$)$_2$), 1.18 (s, 3H, NC(C*H*$_3$)$_2$), 1.25-1.37 (m, 2H, NCCH$_2$C*H*$_2$CH$_2$CN), 1.29 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 1.34 (s, 3H, NC(C*H*$_3$)$_2$), 1.41-1.51 (m, 4H, NCC*H*$_2$CH$_2$C*H*$_2$CN), 2.87 (s, 3H, NC*H*$_3$), 2.99 (sept, *J* = 6.7 Hz, 2H, NC*H*(CH$_3$)$_2$), 3.23 (s, 3H, NC*H*$_3$), 3.62 (dq, *J* = 9.9, 7.0 Hz, 1H, CH$_3$C*H*CH), 4.57 (d, *J* = 9.9 Hz, 1H, C*H*OTMP). - ^{13}C NMR (100 MHz): δ = 16.96 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.04 (q, *C*H$_3$CHCH), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 21.7 (q, NCH(*C*H$_3$)$_2$), 23.9 (q, NCH(*C*H$_3$)$_2$), 32.8 (q, NC(*C*H$_3$)$_2$), 33.7 (q, NC(*C*H$_3$)$_2$), 35.7 (q, N(*C*H$_3$)$_2$), 37.9 (q, N(*C*H$_3$)$_2$), 41.0 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 41.1 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 45.6 (d, N*C*H(CH$_3$)$_2$), 52.5 (d, N*C*HCH), 59.3 (s, N*C*CH$_3$), 60.9 (s, N*C*CH$_3$), 78.9 (d, *C*HOTMP), 173.4 (s, C=O). - *syn*-**3-29b** Detectable resonances: ^{1}H NMR (200 MHz): δ = 2.92 (s, 3H, NC*H*$_3$), 3.23 (s, 3H, NC*H*$_3$), 4.47 (d, *J* = 8.1 Hz, 1H, C*H*OTMP).

***N,N*-Dimethyl-4-(2,2,6,6-tetramethylpiperidin-1-yloxy)-2-butenoic amide 3-30b**



Detectable resonances: ^{1}H NMR (200 MHz): δ = 1.13 (s, 6H, NC(C*H*$_3$)$_2$), 1.14 (s, 6H, NC(C*H*$_3$)$_2$), 1.47 (m, 1H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 3.02 (s, 3H, NC*H*$_3$), 3.10 (s, 3H, NC*H*$_3$), 4.47

(dd, *J* = 4.1, 2.1 Hz, 2H, C*H*$_2$OTMP), 6.54 (dt, *J* = 15.1, 2.0 Hz, 1H, C*H*CON), 6.84 (dt, *J* = 15.3, 4.0 Hz, 1H, C*H*CH$_2$OTMP). - ^{13}C NMR (50 MHz): δ = 17.0 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.1 (q, NC(*C*H$_3$)$_2$), 21.4 (q, NC(*C*H$_3$)$_2$), 32.7 (q, NC(*C*H$_3$)$_2$), 35.6 (q, N(*C*H$_3$)$_2$), 37.3 (q, N(*C*H$_3$)$_2$), 39.5 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 59.8 (s, N*C*CH$_3$), 76.2 (t, *C*H$_2$OTMP), 119.2 (d, *C*HCON), 140.8 (d, *C*HCH$_2$OTMP).

6.5. α-Oxygenations of carbonyl compounds with oxygen

Oxygenation of the enolate of ethyl heptanoate with O_2

BuLi (1.62 mL, 2.6 mmol, 1.6*M* in hexane) was added to a solution of dry *i*Pr$_2$NH (0.366 mL, 2.6 mmol) in 20 mL dry THF at –78 °C. After stirring for 30 min, ethyl heptanoate **3-1d** (316 mg, 2 mmol) dissolved in 2 mL THF was added via syringe and stirring was continued at the same temperature for 30 min. A stream of dry oxygen was bubbled through the solution at –78 °C for 1 h. The reaction was monitored by TLC. The reaction was quenched with eight drops of water and warmed to room temperature. The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel. The solvent removed in vacuo. The substrate was recovered.

Oxygenation of the enolate of ethyl heptanoate with O_2 in the presence of LiCl

To a solution of dry LiCl (169 mg, 4 mmol) and dry *i*Pr$_2$NH (0.183 mL, 1.3 mmol) in 8 mL dry THF BuLi (0.81 mL, 1.3 mmol, 1.6*M* in hexane) was added at –78 °C. The mixture was stirred at –78 °C for 30 min. Ethyl heptanoate **3-1d** (158 mg, 1 mmol) dissolved in 1 mL THF was added via syringe and the reaction mixture was stirred at –78 °C for 30-90 min. A stream of oxygen dried over CaCl$_2$ was bubbled through the solution at –78 °C for 30 min. The mixture was quenched with seven drops of water and warmed to room temperature. The reaction mixture was diluted with diethyl ether and saturated NH$_4$Cl solution was added. The aqueous layer was extracted 3 times with diethyl ether. The combined organic layers were washed twice with water and dried over Na$_2$SO$_4$. The solvent was removed vacuo. Flash chromatography (hexane/ethyl acetate 50:1 gradient to 1:1) afforded mixtures of substrate **3-1d**, β-ketoester **3-35d**,[10a] trimer **3-34d**,[10a] and finally alcohol **3-15d**.[10a] For yields see Table 3.21.

Oxygenation of the enolate of ethyl heptanoate with O_2 in the presence of $FeCp_2PF_6$

BuLi (1.62 mL, 2.6 mmol, 1.6*M* in hexane) was added to a solution of dry *i*Pr$_2$NH (0.366 mL,

2.6 mmol) in 20 mL dry THF at –78 °C. After 30 min, ethyl heptanoate **3-1d** (316 mg, 2 mmol) dissolved in 2 mL THF was added via syringe and stirring was continued at –78 °C for 30 min. A stream of dry oxygen was bubbled through the solution at –78, –40 or –30 °C for 30-60 min (See Table 3.22). Ferrocenium hexafluorophosphate was added in portions, while oxygen bubbling was continued, at –78 °C until a blue-green colour persisted in the reaction mixture for at least 10 min. The reaction was quenched with seven drops of water and warmed to room temperature. It was diluted with diethyl ether and filtered through a pad of silica gel. The solvent was removed in vacuo and the inhomogeneous residue was preadsorbed on silica gel. Flash chromatography with hexane/ethyl acetate 100:1, gradient to 1:1 afforded ferrocene, followed by a mixture of substrate **3-1d**, *meso*-dimer **3-3d**[10a] and β-ketoester **3-35d**, a mixture of *d,l*-dimer **3-3d**,[10a] α-ketoester **3-36d**[167] and trimer **3-34d**, and finally alcohol **3-15d**.

Oxygenation of the enolate of ethyl heptanoate with O_2 in the presence of PhCHO and HMPA

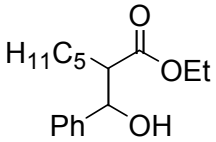
BuLi (0.81 mL, 1.3 mmol, 1.6*M* in hexane) was added to a solution of dry *i*Pr_2NH (0.183 mL, 1.3 mmol) in 9 mL dry THF at –78 °C. After stirring for 30 min, ethyl heptanoate (158 mg, 1 mmol) dissolved in 1 mL THF was added via syringe and the reaction mixture was stirred at –78 °C for 15 min. HMPA (2 mL) was added and stirring was continued for 15 min. A stream of oxygen dried over $CaCl_2$ was bubbled through the solution at –78 °C for 10 min. Benzaldehyde (0.101 mL, 1 mmol) was added and stirring was continued at the same temperature for 30 min. The mixture was quenched with seven drops of water and warmed to room temperature. The reaction mixture was diluted with diethyl ether and saturated NH_4Cl. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with water. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (hexane/ethyl acetate 80:1, gradient to 1:1) afforded mixtures of substrate **3-1d**, β-ketoester **3-35d** and PhCHO, trimer **3-34d** and alcohol **3-15d**. For yields see Table 3.23.

Aldol addition of ethyl heptanoate to benzaldehyde in the presence of HMPA

BuLi (0.81 mL, 1.6*M* in hexane, 1.3 mmol) was added to a solution of dry *i*Pr_2NH (0.183 mL, 1.3 mmol) in 9 mL dry THF at –78 °C. This mixture was stirred for 30 min. Ethyl heptanoate **3-1d** (158 mg, 1 mmol) dissolved in 1 mL THF was added via syringe and the reaction mixture was stirred at –78 °C for 15 min. HMPA (2 mL) was added and stirring was

continued for 15 min. Benzaldehyde (0.101 mL, 1 mmol) was added and the mixture was stirred for 30 min at –78 °C. The reaction was quenched with seven drops of water, warmed to room temperature and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (hexane/ethyl acetate 80:1, gradient to 2:1 afforded **3-35d** in 13% yield and **3-38d** in 49% yield.

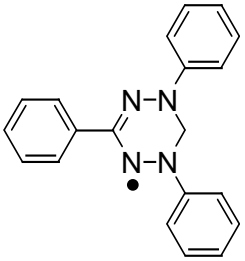
Ethyl (*2R*,3R)- and (*2R*,3S**)-2-(hydroxybenzyl)heptanoate 3-38d**[168]



IR (film): $\tilde{\nu}$ = 3481 (w), 3064 (w), 3031 (w), 2956 (m), 2928 (m), 2859 (w), 1730 (s), 1710 (s), 1453 (m), 1374 (m), 1346 (w), 1270 (w), 1249 (w), 1175 (s), 1156 (s), 1024 (s), 912 (w), 849 (w), 765 (m), 699 (s) cm^{-1}. - MS (EI): *m/z* (%): 264 (5) [M^+], 193 (6) [Ph(OH)CHCHCOOEt]$^+$, 158 (64), 129 (12), 115 (67), 107 (41) [$PhCHOH^+$], 105 (58), 101 (100), 91 (12), 87 (7), 79 (38), 77 (52) [$C_6H_5\bullet^+$], 73 (58) [COOEt]$^+$, 55 (22), 51 (17), 41 (24). - Combustion analysis: $C_{16}H_{24}O_3$ (264.36): calc. C 72.69, H 9.15; found: C 72.31, H 9.12. - ***(2R*,3R*)*-3-38d:** ^{1}H NMR (200 MHz): δ = 0.76 (t, *J* = 6.4 Hz, 3H, $(CH_2)_4CH_3$), 1.02 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.00-1.34 (m, 6H, $CH_3(CH_2)_3CH_2$), 1.60 (m, 2H, CH_2CH), 2.61 (ddd, *J* = 10.0, 5.8, 4.4 Hz, 1H, CHCOOEt), 2.98 (br. s, 1H, OH), 3.95 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.81 (d, *J* = 5.9 Hz, CHOH), 7.21 (m, 5H, arom. CH). - ^{13}C NMR (50 MHz): δ = 13.9 (q, CH_3), 14.0 (q, CH_3), 22.4 (t, CH_2CH_3), 27.1 (t, $CH_2CH_2CH_3$), 31.6 (t, $CH_2CHCOOEt$), 53.1 (d, CHCOOEt), 60.4 (t, OCH_2CH_3), 74.3 (d, CHOH), 126.2 (d, arom. CH), 127.6 (d, arom. CH), 128.2 (d, arom. CH), 141.7 (s, arom. C), 175.0 (s, COOEt). - ***(2R*,3S*)*-3-38d:** ^{1}H NMR (200 MHz): δ = 0.74 (m, 3H, $(CH_2)_4CH_3$), 1.09-1.26 (m, 7H, $CH_3(CH_2)_3CH_2$), 1.13 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.49 (m, 1H, CH_2CH), 2.65 (m, 1H, CHCOOEt), 2.78 (br. s, 1H, OH), 4.08 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.70 (d, *J* = 7.7 Hz, CHOH), 7.23 (m, 5H, arom. CH). - ^{13}C NMR (50 MHz): δ = 13.9 (q, CH_3), 14.2 (q, CH_3), 22.3 (t, CH_2CH_3), 26.7 (t, CH_2CH_2CH), 29.5 (t, $CH_2CH_2CH_3$), 31.4 (t, $CH_2CHCOOEt$), 53.1 (d, CHCOOEt), 60.5 (t, OCH_2CH_3), 75.3 (d, CHOH), 126.4 (d, arom. CH), 127.8 (d, arom. CH), 128.4 (d, arom. CH), 142.2 (s, arom. C), 175.4 (s, COOEt).

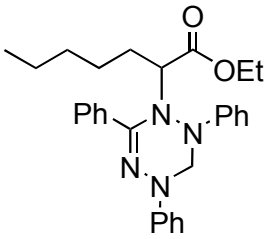
6.6. Coupling of organometallic compounds with the free radical 1,3,5-triphenylverdazyl

2,4,6-Triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-1-yl (1,3,5-triphenylverdazyl) 3-39



To a solution of formazane (3.5 g, 11.7 mmol), BaO (20.2 g, 0.13 mol) and $Ba(OH)_2 \cdot 8H_2O$ (1.2 g, 3.8 mmol) in 120 mL DMF (0.1*M* concentration of substrate) was added CH_3I (35 mL, 0.56 mol) of at 0 °C. The reaction was stirred open to the air at 25 °C for 64 h. During this time the colour of the solution changed to brownish green. The reaction mixture was diluted with CH_2Cl_2 (120 mL) and H_2O (100 mL) and the layers were separated. The organic layer was washed thoroughly with water and finally $NaHSO_4$ to neutral pH, dried over Na_2SO_4 and the solvent was removed in vacuum. The product dissolved in a minimal amount of CH_2Cl_2 was crystallised by addition of CH_3OH. Yield: 2.8 g (76%) as dark green crystals. - m.p. 136-138 °C. - Combustion analysis: $C_{20}H_{17}N_4$ (313.38) calc.: C 76.65, H 5.47, N 17.88; found C 76.30, H 5.46, N 17.98.

Ethyl 2-(2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-1-yl)heptanoate 3-44



BuLi (0.812 mL, 1.3 mmol, 1.6*M* in hexane) was added to a solution of dry *i*Pr_2NH (183 µL, 1.3 mmol) in 10 mL dry THF at –78 °C under nitrogen atmosphere and the mixture was stirred for 30 min. A solution of ethyl heptanoate **3-1d** (158 mg, 1 mmol) dissolved in 1 mL dry THF was added and stirring was continued at –78 °C for 30 min. Verdazyl **3-39** (156 mg, 0.5 mmol) was added and stirred for 5 min until it dissolved. Oxidation was conducted by adding **1-3** (447 mg, 1.35 mmol) in small portions at –78 °C until the colour of the reaction mixture changed to blue-green and persisted in the reaction mixture. The reaction was quenched with 7 drops of water, diluted with diethyl ether, warmed to room temperature and filtered through a pad of silica gel, which was washed with diethyl ether. Flash chromatography with hexane/EtOAc 80:1 gradient to 1:1 afforded ferrocene, a mixture of β-

ketoester **3-35d** and *meso*-dimer **3-3d**, a mixture of *d,l*-dimer **3-3d** and trimer **3-34d**, and finally verdazyl adducts **3-44-I** and **3-44-II** (unknown). For yields see Table 3.25.

Amination in the presence of LiCl

LiCl (264 mg, 6 mmol) was flame dried 3 to 5 times in vacuo. The reaction was subsequently performed similarly according to standard procedure. Flash chromatography with hexane/EtOAc 80:1, gradient to 1:1 afforded ferrocene, followed by a mixture of substrate, *meso*-**3-3d**, *d,l*-**3-3d**, trimer **3-34d** and ethyl heptenoate **3-46**,[169] a mixture of *d,l*-**3-3d** and malonate **3-45**,[170] and finally product **3-44-I** and **3-44-II**. For yields see Table 3.25.

Amination using $CuCl_2$ as the oxidant

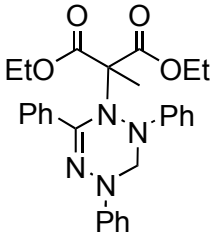
The reaction was performed according to the standard procedure until the oxidation step. $CuCl_2$ (269 mg, 2 mmol, 2 equiv. based on the enolate) was added at once and the reaction mixture was stirred at –78 °C for 20 min. Flash chromatography with hexane/EtOAc 50:1, gradient to 1:1 afforded a mixture of *meso*-dimer and β-ketoester, followed by products **3-44-I** and **3-44-II**. For yields see Table 3.25.

Ethyl 2-(2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-1-yl) heptanoate 3-44:

IR (ATR): $\tilde{\nu}$ = 3062 (w), 3026 (w), 2955 (w), 2928 (w), 2860 (w), 1733 (s), 1596 (s), 1491 (s), 1445 (m), 1378 (w), 1279 (m), 1174 (s), 1113 (w), 1088 (w), 1074 (m), 1026 (m), 994 (w), 967 (w), 941 (w), 918 (w), 877 (w), 770 (s), 745 (s), 689 (s) cm^{-1}. - MS (*m/z*): 307 (7), 292 (8), 263 (6), 201 (5), 156 (100) $[H_7C_4CH{=}CHCOOEt]^{+}\cdot$, 139 (7), 123 (20), 106 (88), 77 (15), 69 (18), 55 (31). - Combustion analysis: $C_{29}H_{34}N_4O_2$ (470.61): calc. C 74.01, H 7.28, N 11.91; found C 74.08, H 7.41, N 11.55. - **3-44-I**: ^{1}H NMR (400 MHz): δ = 0.72 (t, *J* = 6.8 Hz, 3H, C*H*$_3$CH$_2$CH$_2$), 0.93-1.31 (m, 6H, CH$_3$*CH*$_2$*CH*$_2$*CH*$_2$), 1.14 (t, *J* = 7.1 Hz, 3H, *CH*$_3$CH$_2$O), 1.81 (m, 2H, *CH*$_2$CH), 4.04 (m, 2H, OC*H*$_2$), 4.15 (t, *J* = 7.1 Hz, 1H, *CH*COOEt), 4.34 (d, *J* = 11.4 Hz, 1H, NC*H*$_2$N), 5.28 (d, *J* = 11.7 Hz, 1H, NC*H*$_2$N), 6.75 (t, *J* = 7.2 Hz, 1H, arom. C*H*), 6.93 (m, 1H, arom. C*H*), 7.04 (m, 2H, arom. C*H*), 7.17 (m, 6H, arom. C*H*), 7.40 (m, 3H, arom. C*H*), 7.70 (m, 2H, arom. C*H*). - ^{13}C NMR (100 MHz) = 13.8 (q, *C*H$_3$CH$_2$CH$_2$), 14.1 (q, *C*H$_3$CH$_2$O), 22.2 (t, CH$_3$*C*H$_2$CH$_2$), 25.9 (t, *C*H$_2$CH$_2$CH), 27.7 (t, *C*H$_2$CH), 31.5 (t, CH$_3$CH$_2$*C*H$_2$), 60.7 (t, O*C*H$_2$), 63.2 (t, N*C*H$_2$N), 64.2 (d, CH$_2$*C*HN), 113.8 (d, arom. *C*H), 119.7 (d, arom. *C*H), 119.8 (d, arom. *C*H), 123.6 (d, arom. *C*H), 128.2 (d, arom. *C*H), 128.4 (d, arom. *C*H), 128.8 (d, arom. *C*H), 128.9 (d, arom. *C*H), 129.2 (d, arom. *C*H), 135.0 (s, arom. *C*), 144.2 (s, arom. *C*), 146.1 (s, arom. *C*), 150.3 (s, N=*C*Ph), 170.7 (s, *C*OOEt). - **3-44-**

II (unknown compound, possible assignment): ^{1}H NMR (400 MHz): δ = 0.72 (t, *J* = 6.8 Hz, 3H, C*H*$_3$CH$_2$CH$_2$), 0.87 (t, *J* = 7.1 Hz, 3H, *CH*$_3$CH$_2$O), 0.93-1.31 (m, 6H, CH$_3$*CH*$_2$*CH*$_2$*CH*$_2$), 1.81 (m, 1H, *CH*$_2$CH), 1.99 (m, 1H, *CH*$_2$CH), 3.77 (dq, *J* = 10.7, 7.2 Hz, 1H, OC*H*$_2$), 3.89 (dq, *J* = 10.7, 7.2 Hz, 1H, OC*H*$_2$), 4.33 (m, 1H, *CH*COOEt), 4.37 (d, *J* = 11.4 Hz, 1H, NC*H*$_2$N), 5.49 (d, *J* = 11.7 Hz, 1H, NC*H*$_2$N), 6.75 (t, *J* = 7.2 Hz, 1H, arom. C*H*), 6.90 (m, 1H, arom. C*H*), 7.04 (m, 2H, arom. C*H*), 7.17 (m, 6H, arom. C*H*), 7.40 (m, 3H, arom. C*H*), 7.85 (m, 2H, arom. C*H*). - ^{13}C NMR (100 MHz) = 13.5 (q, *C*H$_3$CH$_2$O), 13.8 (q, *C*H$_3$CH$_2$CH$_2$), 22.2 (t, CH$_3$*C*H$_2$CH$_2$), 25.8 (t, *C*H$_2$CH$_2$CH), 27.3 (t, *C*H$_2$CH), 31.3 (t, CH$_3$CH$_2$*C*H$_2$), 60.9 (t, O*C*H$_2$), 64.4 (d, CH$_2$*C*HN), 64.8 (t, N*C*H$_2$N), 113.6 (d, arom. *C*H), 119.5 (d, arom. *C*H), 119.8 (d, arom. *C*H), 123.3 (d, arom. *C*H), 128.2 (d, arom. *C*H), 128.6 (d, arom. *C*H), 128.7 (d, arom. *C*H), 128.9 (d, arom. *C*H), 129.4 (d, arom. *C*H), 134.2 (s, arom. *C*), 143.3 (s, arom. *C*), 146.1 (s, arom. *C*), 149.4 (s, N=*C*Ph), 170.7 (s, *C*OOEt).

Diethyl 2-methyl-2-(2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-1-yl)malonate 3-48



BuLi (0.406 mL, 1.6*M* in hexane, 0.65 mmol) was added to a solution of dry *i*Pr$_2$NH (0.09 mL, 0.65 mmol) in 4 mL dry THF at –78 °C. After stirring at –78 °C for 0.5 h, **3-47** (87 mg, 0.5 mmol) dissolved in 2 mL of THF was added at –78 °C. The mixture was stirred at –78 °C for 0.5 h and **3-39** (148 mg, 0.47 mmol) dissolved in 1 mL of THF was added at 0 °C. The reaction was stirred for 15 min **1-3** (380 mg, 1.15 mmol) was added in small portions at 0 °C. Stirring was continued for 30 min, while the progress of the reaction was monitored by TLC (hexane/EtOAc 5:1). The reaction was quenched with 10 drops of water, diluted with 20 mL diethyl ether, warmed to r.t. and filtered through a pad of silica gel, which was washed with diethyl ether. The solvent was evaporated in vacuo. The inhomogeneous mixture was preadsorbed on silica gel. Flash chromatography with hexane/ethyl acetate 50:1, gradient to 10:1 gave ferrocene, followed by **3-48** as a colourless solid. Yield: 200 mg (87%).

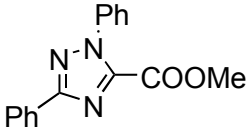
R_f(hexane/EtOAc 5:1) = 0.30. - m.p. = 115-118 °C. - ^{1}H NMR (400 MHz): δ = 1.09 (t, *J* = 7.1 Hz, 3H, OCH$_2$*CH*$_3$), 1.15 (t, *J* = 7.1 Hz, 3H, OCH$_2$*CH*$_3$), 1.63 (s, 3H, C*CH*$_3$), 3.84 (dq, *J* = 10.8, 7.1 Hz, 1H, O*CH*$_2$CH$_3$), 3.98 (dq, *J* = 10.8, 7.1 Hz, 1H, O*CH*$_2$CH$_3$), 4.11 (dq, *J* = 10.8, 7.1 Hz, 1H, O*CH*$_2$CH$_3$), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H, O*CH*$_2$CH$_3$), 4.83 (d, *J* = 12.1 Hz, 1H,

N*CH*$_2$N), 5.61 (d, *J* = 12.1 Hz, 1H, N*CH*$_2$N), 6.85 (tt, *J* = 7.2, 1.1 Hz, 1H, arom. *CH*), 6.93 (tt, *J* = 7.0, 1.3 Hz, 1H, arom. *CH*), 7.13 (m, 2H, arom. *CH*), 7.21-7.29 (m, 6H, arom. *CH*), 7.33 (m, 3H, arom. *CH*), 7.60 (m, 2H, arom. *CH*). - ^{13}C NMR (100 MHz, $CDCl_3$): 13.6 (q, CH_2CH_3), 13.7 (q, CH_2CH_3), 22.9 (t, CCH_3), 59.3 (t, NCH_2N), 61.9 (t, CH_2CH_3), 62.0 (t, CH_2CH_3), 75.3 (s, CCH_3), 113.2 (d, arom. *C*H), 117.4 (d, arom. *C*H), 119.8 (d, arom. *C*H), 122.4 (d, arom. *C*H), 127.7 (d, arom. *C*H), 128.94 (d, arom. *C*H), 128.97 (d, arom. *C*H), 129.02 (d, arom. *C*H), 129.7 (d, arom. *C*H), 135.9 (s, arom. *C*), 141.2 (s, arom. *C*), 145.8 (s, arom. *C*), 148.8 (s, N=*C*(Ph)N), 168.90 (s, *C*O), 168.96 (s, *C*O). - IR (Film): $\tilde{\nu}$ = 3058 (w), 2981 (w), 2901 (w), 1751 (w), 1729 (s), 1598 (m), 1546 (m), 1498 (m), 1468 (w), 1443 (w), 1372 (m), 1268 (s), 1232 (m), 1203 (w), 1180 (m), 1166 (m), 1138 (s), 1079 (w), 1045 (w), 1020 (w), 970 (w), 948 (w), 896 (w), 855 (w), 748 (s), 720 (m), 696 (s) cm^{-1}. - MS (ESI): *m/z* (%) = 995 (100) [2M+Na$^+$], 509 (100) [M+Na$^+$], 487 (43) [M+H$^+$], 404 (8), 313 (64) [1,3,5-triphenylverdazyl$^+$], 195 (9) [(EtOOC)$_2$C=CH$_2$+Na$^+$]. - Combustion analysis: $C_{28}H_{30}N_4O_4$ (486.56): calc. C 69.12, H 6.21, N 11.51; found C 68.43, H 6.21, N 11.87.

Reaction of triphenylverdazyl with methyl acetoacetate 3-49

BuLi (0.625 mL, 1.6*M* in hexane, 1 mmol) was added to a solution of dry *i*Pr$_2$NH (0.141 mL, 1 mmol) in 5 mL dry THF at –78 °C. After stirring at –78 °C for 0.5 h, methyl acetoacetate **3-49** (106 mg, 0.91 mmol) dissolved in 2 mL of THF was added at –78 °C. The mixture was stirred at this temperature for 0.5 h and **3-39** (272 mg, 0.87 mmol) dissolved in 1 mL of THF was added at –78 °C. The mixture was stirred for 15 min. **1-3** (440 mg, 1.33 mmol) was added in small portions at –78 °C. Stirring was continued for 30 min. The progress of the reaction was monitored by TLC (hexane/EtOAc 2:1). The reaction was quenched with 10 drops of water, diluted with 20 mL diethyl ether, warmed to r.t. and filtered through a pad of silica gel. The solvent was evaporated in vacuo. The inhomogeneous mixture was preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate) 50:1 gradient to 10:1 gave ferrocene, followed by **3-51**. Colourless solid. Yield: 190 mg (75%).

Methyl 1,3-diphenyl-1H-1,2,4-triazole-5-carboxylate 3-51



R$_f$(hexane/EtOAc 5:1) = 0.15. - m.p. = 146-148 °C. - ^{1}H NMR (400 MHz): δ = 3.95 (s, 3H, *CH*$_3$), 7.45 (m, 3H, arom. *CH*), 7.53 (s, 5H, arom. *CH*), 8.22 (m, 2H, arom. *CH*). - ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 53.2 (q, *C*H$_3$), 125.7 (d, arom. *C*H), 126.7 (d, arom. *C*H), 128.6 (d,

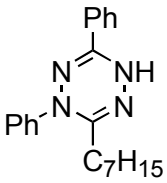
arom. *C*H), 129.0 (d, arom. *C*H), 129.6 (s, arom. *C*), 129.7 (d, arom. *C*H), 129.9 (d, arom. *C*H), 137.9 (s, arom. *C*), 145.0 (s, N=*C*Ph), 157.8 (s, N=*C*COOCH$_3$), 162.0 (*C*OOCH$_3$). - IR (Film): $\tilde{\nu}$ = 3064 (w), 3039 (w), 3004 (w), 2957 (w), 1728 (s), 1597 (w), 1521 (w), 1491 (s), 1464 (m), 1445 (m), 1343 (w), 1303 (s), 1238 (s), 1147 (s), 1107 (s), 1072 (w), 1047 (w), 1018 (m), 947 (w), 908 (w), 824 (m), 789 (w), 755 (s), 719 (s), 686 (s) cm^{-1}. - MS (EI): *m/z* (%) = 279 (100) [M$^+$], 221 (8) [M$^+$ – COOCH$_2$], 194 (34) [PhC=NNPh$^+$], 118 (22), 91 (84) [PhN•$^+$], 77 (11) [Ph•$^+$], 65 (5), 64 (12), 51 (5).

Reaction of octonitrile with verdazyl in the absence of ferrocenium hexafluorphosphate:
BuLi (0.406 mL, 1.6*M* in hexane, 0.65 mmol) was added to a solution of dry *i*Pr$_2$NH (0.09 mL, 0.65 mmol) in 5 mL dry THF at –78 °C. The mixture was stirred for 30 min and octonitrile **3-4b** (0.077 mL, 0.5 mmol) dissolved in 2 mL THF was added at –78 °C. The reaction was stirred at this temperature for 0.5 h and **3-39** (156 mg, 0.5 mmol) dissolved in 2 mL THF was added at 0 °C to the colourless solution. A sudden colour change indicated a fast reaction, the reaction mixture turned shortly to deep green and then immediately to dark red. The reaction was monitored by TLC (hexane/EtOAc 5:1), but no change was observed in the next 30 min. The reaction was quenched with 10 drops of water, diluted with 20 mL diethyl ether and 10 mL CH_2Cl_2 and warmed to r.t. The reaction mixture was filtered through a pad of silica gel with diethyl ether and the solvent was removed in vacuo. The inhomogeneous mixture was preadsorbed on silica. Flash chromatography with hexane/ethyl acetate 20:1 gradient to 2:1 gave a mixture containing a major product that is probably **3-56a** and a minor component which was assigned structure **3-57**. Dark red oil. Yield: 150 mg **3-56a:3-57** 4.7:1.

Reaction of octonitrile with verdazyl in the presence of ferrocenium hexafluorphosphate:
To the ketene iminate solution, prepared as above, was added **3-39** (156 mg, 0.5 mmol) dissolved in 2 mL of THF at 0 °C to the colourless solution. A sudden colour change indicated a fast reaction, the reaction mixture turned shortly to deep green and then immediately to dark red. After stirring for 5 min, **1-3** (590 g, 1.8 mmol) was added in portions and the reaction was stirred for further 35 min. The reaction was monitored by TLC (hexane/EtOAc 5:1), but the only new spot on TLC was that of ferrocene. The reaction was quenched with 10 drops of water, diluted with 20 mL diethyl ether and 10 mL CH_2Cl_2 and warmed to r.t. The reaction mixture was filtered through a pad of silica gel with diethyl ether and the solvent was removed in vacuum. The inhomogeneous mixture was preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate 20:1, gradient to 1:1) gave a mixture

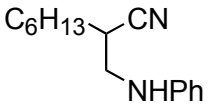
containing a major unknown product that is probably **3-56a** and a minor component which was assigned structure **3-57**. Dark red oil. Yield: 60 mg, **3-56a:3-57** 7:1.

6-Heptyl-1,3-diphenyl-1,4-dihydro-1,2,4,5-tetrazine 3-56a



R_f(hexane/EtOAc 5:1) = 0.30. - Detectable resonances: ^{1}H NMR (200 MHz): δ = 0.85 (t, *J* = 6.8 Hz, 3H, C*H*$_3$CH$_2$), 1.21-1.41 (m, 8H, CH$_3$(C*H*$_2$)$_4$), 1.78 (m, 2H, N=CCH$_2$C*H*$_2$), 2.82 (m, 2H, N=CC*H*$_2$), 7.34-7.57 (m, 8H, arom. *CH*), 8.15 (m, 2H, arom. *CH*). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (q, *C*H$_3$CH$_2$), 22.3 (t, CH$_3$*C*H$_2$), 26.5 (t, *C*H$_2$), 27.8 (t, *C*H$_2$), 28.7 (t, *C*H$_2$), 31.2 (t, *C*H$_2$), 125.1 (d, arom. *C*H), 126.3 (d, arom. *C*H), 128.4 (d, arom. *C*H), 128.8 (d, arom. *C*H), 129.0 (d, arom. *C*H), 129.3 (d, arom. *C*H), 130.8 (s, arom. *C*), 137.5 (s, arom. *C*), 157.0 (s, N=*C*), 161.3 (s, N=*C*).

2-((Phenylamino)methyl)octonitrile 3-57



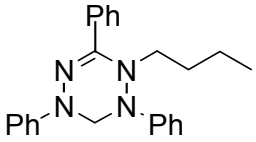
R_f(hexane/EtOAc 5:1) = 0.30. - Detectable resonances: ^{1}H NMR (200 MHz): δ = 0.85 (m, 3H, C*H*$_3$CH$_2$), 1.21-1.67 (m, 11H, CH$_3$(C*H*$_2$)$_5$C*H*CN), 3.38 (m, 2H, CHC*H*$_2$NHPh), 4.02 (br. s, 1H, N*H*Ph), 6.60 (d, *J* = 7.6 Hz, 2H, arom. *CH*), 6.75 (t, *J* = 7.3 Hz, 1H, arom. *CH*), 7.20 (dd, *J* = 8.3, 7.5 Hz, 2H, arom. *CH*). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (q, *C*H$_3$CH$_2$), 22.3 (t, CH$_3$*C*H$_2$), 29.6 (t, *C*H$_2$), 31.3 (t, *C*H$_2$), 32.2 (d, *C*HCN), 45.5 (t, *C*H$_2$NHPh), 112.8 (d, arom. *C*H), 118.2 (s, CH*C*N).

6.7. Reactions of 1,3,5-triphenylverdazyl with organometallic reagents

Standard procedure: BuLi (0.156 mL, 1.6*M* in hexane, 0.25 mmol) was added to a solution of **3-39** (156 mg, 0.5 mmol) in 8 mL dry THF at –78 °C. The colour of the solution changed form deep green to brown. A stream of dry oxygen was bubbled through the solution for a few minutes, during which the dark green colour reappeared. The solution was purged with nitrogen, and titrated dropwise with BuLi. The addition was stopped when the colour changed from deep green to brown. A stream of dry stream of oxygen was bubbled through the solution until the brown colour changed back to green. The reaction mixture was again purged

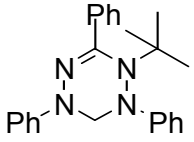
with nitrogen. This was repeatedly performed until the brown colour of the mixture persisted for at least 20 min, and the amount of BuLi reached a total of 1.216 mL (1.9 mmol, 3.9 equiv.). The progress of the reaction was monitored by TLC (hexane/EtOAc 5:1). The reaction was quenched with 10 drops of water, diluted with diethyl ether and warmed to r.t. This solution was filtered through a pad of silica gel, which was washed with diethyl ether. The solvent was removed in vacuo and the inhomogenous mixture was preadsorbed on silica. Flash chromatography (hexane/EtOAc 40:1 gradient to 1:1) afforded **3-58a** (160 mg, 85%) as colourless solid.

1-Butyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine 3-58a



R_f(hexane/EtOAc 5:1) = 0.60. - m.p. 108-110 °C. - ^{1}H NMR (200 MHz): δ = 0.76 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 1.22 (sext, *J* = 7.3 Hz, 2H, CH$_3$C*H*$_2$), 1.65 (quint, *J* = 7.3 Hz, 2H, CH$_3$CH$_2$C*H*$_2$), 2.60 (m, 1H, CH$_2$C*H*$_2$N), 3.22 (m, 1H, CH$_2$C*H*$_2$N), 4.24 (br. d, *J* = 12.1 Hz, 1H, NC*H*$_2$N), 5.54 (br. d, *J* = 11.8 Hz, 1H, NC*H*$_2$N), 6.77 (m, 2H, arom. *CH*), 7.09 (m, 8H, arom. *CH*), 7.28 (m, 3H, arom. *CH*), 7.72 (m, 2H, arom. *CH*). - ^{13}C NMR (50 MHz, CDCl$_3$): δ = 13.9 (q, *C*H$_3$CH$_2$), 20.1 (t, CH$_3$*C*H$_2$), 29.6 (t, *C*H$_2$CH$_2$N), 55.1 (t, CH$_2$*C*H$_2$N), 57.7 (t, N*C*H$_2$N), 113.4 (d, arom. *C*H), 117.0 (d, arom. *C*H), 119.9 (d, arom. *C*H), 121.9 (d, arom. *C*H), 127.2 (d, arom. *C*H), 128.4 (d, arom. *C*H), 129.0 (d, 3C, arom. *C*H), 135.2 (s, arom. *C*), 144.6 (s, arom. *C*), 145.9 (s, arom. *C*), 149.0 (s, N=*C*(Ph)N). - IR (film): $\tilde{\nu}$ = 3061 (w), 3027 (w), 2963 (w), 2924 (w), 2858 (w), 1594 (s), 1554 (m), 1491 (s), 1467 (m), 1444 (m), 1379 (m), 1334 (m), 1311 (m), 1285 (m), 1203 (m), 1181 (m), 1146 (m), 1115 (w), 1068 (m), 1027 (m), 994 (m), 975 (w), 951 (w), 919 (w), 833 (w), 854 (m), 787 (w), 744 (s), 688 (s) cm^{-1}. - MS (EI): *m/z* (%) = 370 (100) [M$^+$], 313 (29) [1,3,5-triphenylverdazyl$^+$], 263 (9), 235 (9), 194 (10), 160 (19), 104 (100) [CH=NPh]$^+$, 91 (22), 77 (36), 57 (5) [Bu]$^+$.

1-*tert*-Butyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine 3-58b

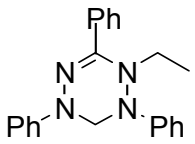


According to the standard procedure **3-58b** was synthesised by the addition of *t*BuLi (1.4*M* in pentane) to a solution of **3-39** (156 mg, 0.5 mmol) in THF at –78 °C. The deep green solution changed to brown after the addition of a total amount of 2.1 equiv. *t*BuLi (1.05 mL, 1.47

mmol). Titration with *t*BuLi, followed by reoxidation by an oxygen stream and finally purging nitrogen was performed until a total of 2.69 mmol *t*BuLi (1.925 mL) was added. Flash chromatography (hexane/EtOAc 40:1, gradient to 1:1) afforded **3-58b** (90 mg, 48% yield) as a colourless solid.

R_f(hexane/EtOAc 5:1) = 0.15. - m.p. 189-190 °C. - ^{1}H NMR (200 MHz): δ = 1.25 (s, 9H, NC(C*H*$_3$)$_3$), 4.73 (d, *J* = 12.3 Hz, 1H, NC*H*$_2$N), 5.78 (d, *J* = 12.3 Hz, 1H, NC*H*$_2$N), 6.86 (m, 2H, arom. *CH*), 7.11-7.26 (m, 8H, arom. *CH*), 7.33 (m, 3H, arom. *CH*), 7.63 (m, 2H, arom. *CH*). - ^{13}C NMR (50 MHz): δ = 30.1 (q, NC(*C*H$_3$)$_3$), 60.3 (s, N*C*(CH$_3$)$_3$), 62.0 (t, N*C*H$_2$N) 112.8 (d, arom. *C*H), 117.1 (d, arom. *C*H), 119.6 (d, arom. *C*H), 121.6 (d, arom. *C*H), 127.8 (d, arom. *C*H), 128.4 (d, arom. *C*H), 128.9 (d, arom. *C*H), 129.0 (d, 3C, arom. *C*H), 129.1 (d, arom. *C*H), 139.5 (s, arom. *C*), 142.9 (s, arom. *C*), 145.5 (s, arom. *C*), 150.0 (s, N=*C*(Ph)N).

1-Ethyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine 3-58c



Synthesis of 3-58c from 3-39 and EtMgBr

According to the standard procedure, **3-58c** was synthesised from **3-39** (313 mg, 1 mmol) and EtMgBr (1.83 mmol, 1.83 mL of a 1*M* solution in THF) at –78 °C. Flash chromatography (hexane/EtOAc 20:1, gradient to 2:1) afforded 160 mg (47%) **3-58c** as a colourless solid.

Synthesis of 3-58c from 3-39 and Et_2Zn

According to the standard procedure, **3-58c** was synthesised from **3-39** (156.5 mg, 0.5 mmol) and Et_2Zn (0.545 mmol, 0.545 mL of a 1*M* solution in diethyl ether) at 0 °C. Flash chromatography with hexane/EtOAc 40:1, gradient to 1:1 afforded 80 mg (47% yield) **3-58c** as a colourless solid.

R_f(hexane/EtOAc 5:1) = 0.55. - m.p. 132-134 °C. - ^{1}H NMR (200 MHz): δ = 1.22 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$N), 2.76 (br. s, 1H, NC*H*$_2$CH$_3$), 3.35 (br. s, 1H, NC*H*$_2$CH$_3$), 4.31 (d, *J* = 11.9 Hz, 1H, NC*H*$_2$N), 5.62 (d, *J* = 11.0 Hz, 1H, NC*H*$_2$N), 6.82 (m, 2H, arom. C*H*), 7.14 (m, 8H, arom. C*H*), 7.36 (m, 3H, arom. C*H*), 7.73 (m, 2H, arom. C*H*). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.9 (q, CH$_2$*C*H$_3$), 49.8 (t, N*C*H$_2$CH$_3$), 57.8 (t, N*C*H$_2$N), 113.5 (d, arom. *C*H), 117.0 (d, arom. *C*H), 120.0 (d, arom. *C*H), 122.0 (d, arom. *C*H), 127.2 (d, arom. *C*H), 128.5 (d, arom. *C*H), 129.1 (d, arom. *C*H), 135.5 (s, arom. *C*), 144.5 (s, arom. *C*), 146.0 (s, arom.

C), 149.5 (s, N=*C*(Ph)N). - IR (ATR): $\tilde{\nu}$ = 3057 (w), 3034 (w), 2980 (w), 2933 (w), 2887 (w), 2855 (w), 1595 (s), 1547 (w), 1491 (s), 1463 (m), 1441 (w), 1386 (w), 1357 (w), 1331 (m), 1304 (w), 1276 (m), 1188 (m), 1146 (m), 1058 (m), 1024 (m), 992 (w), 960 (m), 919 (w), 874 (w), 831 (w), 762 (s), 741 (s), 685 (s), 666 (m) cm^{-1}. - MS (EI): *m/z* (%) = 342 (100) [M^+], 313 (11) [1,3,5-triphenylverdazyl•$^+$], 132 (29), 104 (37) [(N=CPh)•$^+$], 77 (19), 57 (8).

6.8. Oxidative dimerisations of carbonyl compounds

Dimerisation of ethyl valerate (General procedure):

BuLi (1.22 mL, 1.95 mmol, 1.6*M* in hexane) was added to a solution of diisopropylamine (0.275 mL, 1.95 mmol) in 14 mL of dry THF at –78 °C. After stirring for 30 min, ethyl valerate **3-1a** (195 mg, 1.5 mmol) dissolved in 1 mL of THF was added at –78 °C and stirring was continued for 30 min. Ferrocenium hexafluorophosphate **1-3** was added in portions at –78 °C as the blue colour of the oxidant vanished in the reaction mixture. Addition was continued to a total amount of 880 mg (2.6 mmol) when a deep blue colour persisted in the solution for 10 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through a pad of silica gel. The solvent was concentrated in vacuo and the crude mixture was preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate 80:1, gradient to 10:1) afforded ferrocene, followed by *meso*-**3-3a**,[25] a mixture of *meso*-**3-3a** and *d,l*-**3-3a**,[25] and finally *d,l*-**3-3a**. Yield: 175 mg (89%) *meso*-**3-3a**:*d,l*-**3-3a** 2.5:1 (R_f(hexane/EtOAc 10:1) = 0.38, 0.34).

Dimerisation of ethyl valerate 3-1a with addition of the oxidant in one portion

The enolate of **3-1a** (195 mg, 1.5 mmol) was generated according to the general procedure. Ferrocenium hexafluorophosphate **1-3** (993 mg, 3 mmol) was added in one portion at –78 °C and stirring was continued for 20 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. Workup and purification were performed according to the general procedure. Yield: 117 mg (60%) *meso*-**3-3a**:*d,l*-**3-3a** 1.5:1; 2.9 mg of trimer **3-34a** (1.7%) was detected in the NMR spectra.

Dimerisation of 3-1a at –20 °C

BuLi (1.5 mL, 1.6*M* in hexane, 2.4 mmol) was added to a solution of diisopropyl amine (0.338 mL, 2.4 mmol) in 17 mL dry THF at –78 °C. After stirring for 30 min, **3-1a** (240 mg, 1.8 mmol) dissolved in 1 mL of THF was added at –78 °C and stirring was continued for 30

min. Ferrocenium hexafluorophosphate **1-3** was added in portions at –20 °C as long as the blue colour of the oxidant disappeared in the reaction mixture. Addition was continued to a total amount of 880 mg (2.6 mmol) when a deep blue colour persisted in the solution for 10 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through silica gel. The solvent was concentrated in vacuo and the crude mixture was preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate 80:1, gradient to 10:1) afforded ferrocene, followed by *meso*-**3-3a**, a mixture of *meso*-**3-3a** and *d,l*-**3-3a**, and finally a mixture of *d,l*-**3-3a** and trimer **3-34a**. Yield: 123 mg (53%) *meso*-**3-3a**:*d,l*-**3-3a** 2.5:1; 51 mg (25%) of trimer **3-34a**.

Dimerisation of 3-1a in DME

The reaction was performed according to the general procedure in 15 mL of dry DME. Flash chromatography (hexane/ethyl acetate 80:1 gradient to 10:1) afforded ferrocene, followed by *meso*-**3-3a**, a mixture of *meso*-**3-3a** and *d,l*-**3-3a**, and finally a mixture of *d,l*-**3-3a** and trimer **3-34a**. Yield: 106 mg (54%) *meso*-**3-3a**:*d,l*-**3-3a** 1:1.8; 2.2 mg (2%) trimer **3-34a**.

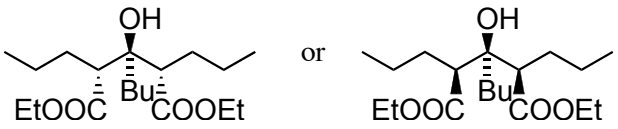
Dimerisation of 3-1a in 85% DME and 15% HMPA

The reaction was performed according to the general procedure in 15 mL of dry DME/HMPA 5.7:1. Flash chromatography (hexane/ethyl acetate 80:1 gradient to 10:1) afforded ferrocene, followed by a mixture of *meso*-**3-3a** and *d,l*-**3-3a**. Yield: 12 mg (16%). The ratio *meso*-**3-3a**:*d,l*-**3-3a** could not be calculated from the NMR spectra.

Dimerisation of 3-1a in DME in the presence of 0.4 equivalents of TEMPO

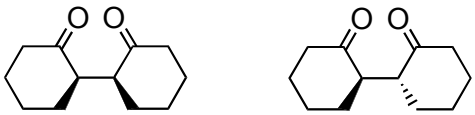
The deprotonation of **3-1a** (195 mg, 1.5 mmol) was performed in 15 mL of dry DME according to the general procedure. TEMPO **1-2** (93.6 mg, 0.6 mmol) was added at –78 °C and the reaction mixture was stirred for 5 min. Addition of 550 mg (1.7 mmol) of **1-3** and workup were performed according to the general procedure. Flash chromatography (hexane/ethyl acetate 80:1 gradient to 10:1) afforded ferrocene, followed by **3-2a**, a mixture **3-2a**, *meso*-**3-3a** and β-ketoester **3-35a**, *d,l*-**3-3a**, and finally a mixture of *d,l*-**3-3a** and trimer **3-34a**. Yield by NMR: 124 mg (29%) of **3-2a**; 78 mg (40%) *meso*-**3-3a**:*d,l*-**3-3a** 1:1.5; β-ketoester **3-35a** 12 mg (6%); 46 mg (23%) trimer **3-34a**.

4,6-Diethyl (4S*,5S*,6R*)-5-butyl-5-hydroxynonane-4,6-dioate (*meso*-**3-34a**):



^{1}H NMR (400 MHz): δ = 0.87 (m, 6H, 2x$CH_2CH_2CH_3$), 1.24 (t, *J* = 7.1 Hz, 6H, 2xOCH_2CH_3), 1.07-1.38 (m, 8H, 2x$CHCH_2CH_2CH_3$, $CH_3(CH_2)_2CH_2COH$), 1.47 (m, 2H, $CHCH_2$), 1.62 (m, 2H, CH_2COH), 1.74 (m, 2H, $CHCH_2$), 2.57 (dd, *J* = 11.7, 2.9 Hz, 2H, 2xCHCOH), 4.06-4.18 (m, 4H, OCH_2). - ^{13}C NMR (100 MHz): δ = 13.9 (q, $CH_3CH_2CH_2$), 14.2 (q, OCH_2CH_3), 21.3 (t, $CHCH_2CH_2CH_3$), 23.4 (t, $CH_3CH_2(CH_2)_2$), 25.8 (t, CH_2CH_2COH), 29.7 (t, $CHCH_2$), 34.7 (t, CH_2COH), 52.9 (d, CHCOH), 60.4 (t, OCH_2CH_3), 75.5 (s, COH), 175.3 (s, CO).

2,2'-Bi(2-oxocyclohexyl) 3-12f



meso-**3-12f** *dl*-**3-12f**

Dimerisation of cyclohexanone according to the general procedure

The reaction was performed with **3-10f** (147 mg, 1.5 mmol) according to the general procedure. Flash chromatography (hexane/ethyl acetate 50:1 gradient to 2:1) afforded ferrocene, followed by *d,l*-**3-12f**, a mixture of *d,l*-**3-12f** and *meso*-**3-12f**, and finally *meso*-**3-12f**. Yield: 125 mg (86%) *meso*-**3-12f**:*d,l*-**3-12f** 1:1.1.

Dimerisation of cyclohexanone 3-10f in the presence of LiCl

LiCl (399.5 mg, 9.4 mmol) was flame dried 3-4 times in vacuo. After cooling, it was dissolved in 19 mL of dry THF under a nitrogen atmosphere. Dry diisopropylamine (0.336 mL, 2.6 mmol) and BuLi (1.625 mL, 1.6*M* in hexane, 2.6 mmol) were added, at –78 °C. After stirring for 30 min, **3-10f** (196 mg, 2 mmol) dissolved in 1 mL of THF was added at –78 °C and stirring was continued for 30 min **1-3** was added in portions at –78 °C as the blue colour of the oxidant vanished in the reaction mixture. Addition was continued to a total amount of 1.01 g (3.05 mmol) when a deep blue colour persisted in the solution for 10 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through silica gel. The solvent was concentrated in vacuo and the crude mixture was preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate

50:1, gradient to 2:1) afforded ferrocene, followed by *d,l*-**3-12f**, and finally a mixture of *d,l*-**3-12f** and *meso*-**3-12f**. Yield: 110 mg (56%) *meso*-**3-12f**:*d,l*-**3-12f** 1.2:1.

Dimerisation of cyclohexanone in the presence of HMPA

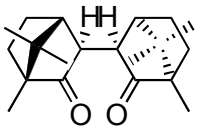
BuLi (1.625 mL, 1.6*M* in hexane, 2.6 mmol) was added to a solution of dry diisopropylamine (0.336 mL, 2.6 mmol) in 19 mL of dry THF at –78 °C. After stirring for 30 min, **3-10f** (196 mg, 2 mmol) dissolved in 1 mL of THF was added at –78 °C and stirring was continued for 30 min. HMPA (2.1 mL, 12 mmol) was added via syringe and the solution was stirred for 5 min. **1-3** was added in portions at –78 °C as the blue colour of the oxidant vanished in the reaction mixture. Addition was continued to a total amount of 980 g (3 mmol) when a deep blue colour persisted in the solution for 10 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through a pad of silica gel. The solvent was concentrated in vacuo and the crude mixture was preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate 50:1, gradient to 2:1 afforded ferrocene), followed by *d,l*-**3-12f**, and finally a mixture of *d,l*-**3-12f** and *meso*-**3-12f**. Yield: 130 mg (67%) *meso*-**3-12f**:*d,l*-**3-12f** 1:1.

IR (ATR): $\tilde{\nu}$ = 2932 (m), 2861 (w), 1700 (s), 1449 (w), 1312 (w), 1218 (w), 1129 (m), 1022 (w), 833 (w) cm^{-1}. - MS (EI) *m/z* (%): 194 (34) [M^+], 176 (17) [M^+-H_2O], 169 (12), 148 (39), 137 (25), 125 (20), 111 (36) [$M+H^+-2CH_2CO\cdot]^+$, 98 (100) [cyclohexanone + H]$^+$, 81 (50), 69 (59), 57 (76). Combustion analysis: $C_{12}H_{18}O_2$ (194.27): calc. C 74.19, H 9.34; found: C 73.95, H 9.48. - *d,l*-**3-12f**: R_f(hexane/ethyl acetate 2:1) = 0.48. - ^{1}H NMR (400 MHz): δ = 1.26 (dq, *J* = 3.6, 12.6 Hz, 2H, CHC*H*$_2$), 1.48-1.60 (m, 2H, C*H*$_2$CH$_2$CO), 1.65 (tq, *J* = 3.5, 12.9 Hz, 2H, C*H*$_2$CH$_2$CH), 1.83 (m, 2H, C*H*$_2$CH$_2$CH), 1.95-2.07 (m, 4H, CHC*H*$_2$CH$_2$C*H*$_2$), 2.33 (m, 4H, C*H*$_2$CO), 2.83 (m, 2H, C*H*CO). - ^{13}C NMR (100 MHz): δ = 25.4 (t, *C*H$_2$), 28.0 (t, *C*H$_2$), 30.1 (t, *C*H$_2$), 42.3 (t, *C*H$_2$CO), 48.9 (d, *C*HCO), 211.8 (s, CO). - *meso*-**3-12f**: R_f(hexane/ethyl acetate 2:1) = 0.42. - ^{1}H NMR (400 MHz): δ = 1.53-1.76 (m, 6H), 1.86-2.11 (m, 6H), 2.27 (m, 2H, C*H*$_2$CH), 2.39 (m, 2H, C*H*$_2$CO), 2.63 (m, 2H, C*H*CO). - ^{13}C NMR (100 MHz): δ = 24.8 (t, *C*H$_2$), 26.3 (t, *C*H$_2$), 28.9 (t, *C*H$_2$), 41.6 (t, *C*H$_2$CO), 50.1 (d, *C*HCO), 210.5 (s, CO).

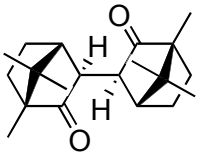
Bi(1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-yl)s 3-12h

BuLi (0.812 mL, 1.6*M* in *n*-hexane, 1.3 mmol) was added to a solution of dry *i*Pr$_2$NH (0.183 mL, 1.3 mmol) in 9 mL dry THF at −78 °C under a nitrogen atmosphere. After stirring for 20 min a solution of 1-*(R)*-camphor **3-10h** (152 mg, 1 mmol) in 1 mL dry THF was added. After stirring for 30 min at −78 °C, **1-3** was added in portions as it was consumed. Addition was

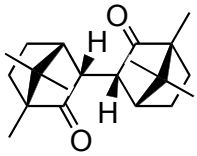
performed until the blue colour of the mixture persisted for at least 10 min (total amount 440 mg, 1.3 mmol). The reaction was monitored by TLC. The reaction mixture was quenched with a few drops of water, warmed to r.t., and diluted with diethyl ether. The mixture was filtered through a pad of silica gel, concentrated in vacuum and preadsorbed on a silica gel. Flash chromatography (hexane/ethyl acetate 5:1, gradient to 1:1) afforded ferrocene, followed by a mixture of *3,3'-exo,endo*-**3-12h** and *3,3'-endo,endo*-**3-12h**, which were not separable, and finally *3,3'-exo,exo*-**3-12h.** Yield: 66% (100 mg), d.r. *3,3'-exo,endo*-**3-12h:***3,3'-endo,endo*-**3-12h:***3,3'-exo,exo*-**3-12h** 2.2:1.8:1. A second experiment with 2 mmol of 1-*(R)*-camphor **3-10h** under similar conditions afforded 200 mg of dimer (66% yield) with a d.r. *3,3'-exo,endo*-**3-12h:***3,3'-endo,endo*-**3-12h:***3,3'-exo,exo*-**3-12h** 1.7:1:1.8. Isomers *3,3'-exo,endo*-**3-12h** and *3,3'-endo,endo*-**3-12h** were not separable and were analysed as a mixture.



3,3'-exo,endo-**3-12h**



3,3'-exo,exo-**3-12h**



3,3'-endo,endo-**3-12h**

IR (ATR): $\tilde{\nu}$ = 2958 (m), 2931 (m), 2872 (w), 1730 (s), 1482 (w), 1447 (w), 1392 (w), 1373 (w), 1323 (w), 1266 (w), 1044 (m), 1026 (m), 749 (w), 655 (w), 568 (w) cm^{-1}. - MS (EI) *m/z* (%): 302 (89) [M^+], 274 (100) [$M^+-CH_2=CH_2$], 259 (67) [$M^+-(CH_3)_2CH$], 246 (10) [$M^+-2xCH_2=CH_2$], 231 (27), 203 (18), 193 (27) [$MH^+-1,5,5$-trimethyl-1,3-cyclopentadiene], 191 (24), 163 (28), 151 (56) [*(R)*-Camphor$^+$], 123 (22) [*(R)*-Camphor$-CH_2=CH_2$], 121 (26), 108 (47) [1,5,5-trimethyl-1,3-cyclopentadiene], 83 (54) [COCH=CHCO· + H]$^+$, 79 (31), 55 (56) [$CH_3C=C=O^+$], 43 (15) [$(CH_3)_2CH^+$]. - Combustion analysis: $C_{20}H_{30}O_2$ (302.45): calc. C 79.42, H 10.00; found: C 79.47, H 10.38.

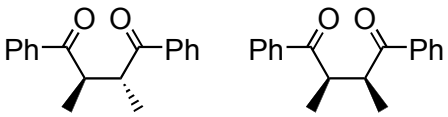
***(1R,1R',3R,3R',4R,4R')*-Bi(1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-yl) (*3,3'-endo,endo*-3-12h)**: R_f(hexane/ethyl acetate 5:1) = 0.59. - m.p. 20-22 °C. - ^{1}H NMR (400 MHz): δ = 0.85 (s, 12H, C(CH_3)$_2$), 0.97 (s, 6H, CH_2CCH_3), 1.60 (m, 4H, CH_2CH_2CH), 1.79 (m, 4H, $CHCH_2CH_2$), 1.96 (m, 2H, CH_2CHCH), 2.43 (m, 2H, $CHCO$). - ^{13}C NMR (100 MHz): δ = 9.7 (q, CH_2CCH_3), 19.4 (q, C(CH_3)$_2$), 19.9 (q, C(CH_3)$_2$), 22.2 (t, CH_2CCH_3), 30.5 (t, $CHCH_2CH_2$), 45.7 (s, CCH_3), 49.0 (d, $CHCHCO$), 49.1 (d, $CHCO$), 59.2 (s, CCH_3), 218.7 (s, CO).

***(1R,1R',3R,3S',4R,4R')*-Bi(1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-yl) (*3,3'-endo,exo*-3-12h)**: R_f(hexane/ethyl acetate 5:1) = 0.43. - m.p. 21-22 °C. - ^{1}H NMR (400 MHz): δ = 0.77 (s, 3H, C(CH_3)$_2$), 0.82 (s, 3H, C(CH_3)$_2$), 0.85 (s, 6H, C(CH_3)$_2$), 0.91 (s, 3H, CH_2CCH_3), 0.95 (s, 3H, CH_2CCH_3), 1.21 (m, 1H, CH_2CCO *endo*-part), 1.38 (m, 2H, $CHCH_2CH_2$ *exo*-part), 1.61

(m, 2H, C*H*$_2$CCO *endo*-part+*exo*-part), 1.76 (m, 1H, C*H*$_2$CH *endo*-part), 1.87 (m, 2H, C*H*$_2$C*H*CHCO *endo*-part), 2.01 (m, 1H, C*H*$_2$CH *exo*-part), 2.35 (t, *J* = 4.3 Hz, 1H, C*H*CO *exo*-part), 2.42 (m, 1H, C*H*CO *endo*-part), 2.67 (d, *J* = 4.0 Hz, 1H, C*H*CHCO *exo*-part). - ^{13}C NMR (100 MHz): δ = 9.51 (q, CH$_2$C*C*H$_3$), 9.55 (q, CH$_2$C*C*H$_3$), 19.1 (q, C(*C*H$_3$)$_2$), 19.5 (q, C(*C*H$_3$)$_2$), 20.3 (q, C(*C*H$_3$)$_2$), 21.2 (t, *C*H$_2$CH *endo*-part), 21.8 (q, C(*C*H$_3$)$_2$), 28.9 (t, CH*C*H$_2$CH$_2$ *exo*-part), 29.2 (t, *C*H$_2$CCH$_3$ *exo*-part), 30.6 (t, *C*H$_2$CCH$_3$ *endo*-part), 45.2 (s, *C*CH$_3$), 46.3 (s, *C*CH$_3$), 46.5 (d, *C*HCHCO *exo*-part), 46.6 (d, *C*HCO *exo*-part), 51.6 (d, *C*HCO *endo*-part), 51.7 (d, *C*HCHCO *endo*-part), 57.4 (s, *C*CH$_3$), 58.4 (s, *C*CH$_3$), 219.6 (s, CO), 220.6 (s, CO).

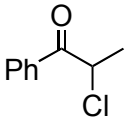
***(1R,1R',3S,3S',4R,4R')*-Bi(1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-yl) (*3,3'-exo,exo*-3-12h)**: R$_f$(hexane/ethyl acetate 5:1) = 0.59. - m.p. 20-22 °C. - ^{1}H NMR (400 MHz): δ = 0.72 (s, 6H, C(C*H*$_3$)$_2$), 0.87 (s, 6H, CH$_2$CC*H*$_3$), 0.90 (s, 6H, C(C*H*$_3$)$_2$), 1.28 (ddd, *J* = 12.5, 9.0, 3.7 Hz, 2H, CH$_2$C*H*$_2$CH), 1.48-1.64 (m, 4H, C*H*$_2$CCO), 1.95 (ddd, *J* = 16.7, 10.9, 4.5 Hz, 2H, CHC*H*$_2$CH$_2$), 2.00 (s, 2H, C*H*CO), 2.08 (d, *J* = 4.1 Hz, 2H, CH$_2$C*H*CH). - ^{13}C NMR (100 MHz): δ = 9.4 (q, CH$_2$C*C*H$_3$), 20.0 (q, C(*C*H$_3$)$_2$), 21.0 (q, C(*C*H$_3$)$_2$), 28.8 (t, *C*H$_2$CCH$_3$), 29.0 (t, CH*C*H$_2$CH$_2$), 46.8 (d, *C*HCHCO), 54.2 (d, *C*HCO), 57.3 (s, *C*CH$_3$), 219.3 (s, CO).

***d,l*- and *meso*-2,3-Dimethyl-1,4-diphenyl-1,4-butandione 3-12a**



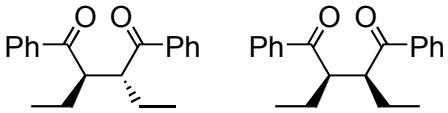
Combustion analysis: C$_{18}$H$_{18}$O$_2$ (266.33): calc. C 81.17, H 6.81; found C 80.89, H 6.90. - ***d,l*-3-12a**: *R*$_f$ = 0.4 (hexane/EtOAc 5:1). - ^{1}H NMR (200 MHz): δ = 1.19 (m, 6H, CHC*H*$_3$), 3.89 (m, 2H, C*H*), 7.16-7.48 (m, 6H, arom. C*H*), 7.93 (m, 4H, arom. C*H*). - ^{13}C NMR (50 MHz): δ = 15.5 (q, *C*H$_3$), 43.6 (d, *C*H), 128.4 (d, arom. *C*H), 128.6 (d, arom. *C*H), 132.9 (d, arom. *C*H), 136.1 (s, arom. *C*), 204.2 (s, *C*O). - ***meso*-3-12a**: *R*$_f$ = 0.5 (hexane/EtOAc 5:1). - ^{1}H NMR (200 MHz): δ = 1.08 (m, 6H, CHC*H*$_3$), 3.98 (m, 2H, C*H*), 7.38-7.58 (m, 6H, arom. C*H*), 7.99 (m, 4H, arom. C*H*). - ^{13}C NMR (50 MHz): δ = 17.4 (q, *C*H$_3$), 43.3 (d, *C*H), 128.4 (d, arom. *C*H), 128.8 (d, arom. *C*H), 133.3 (d, arom. *C*H), 136.8 (s, arom. *C*), 203.7 (s, *C*O).

1-Phenyl-2-chloro-1-propanone 3-63a[171]



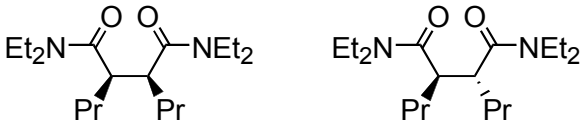
^{1}H NMR (400 MHz): δ = 1.74 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 5.26 (d, *J* = 6.7 Hz, 1H, C*H*), 7.44-7.65 (m, 3H, arom. C*H*), 8.04 (m, 2H, arom. C*H*). - ^{13}C NMR (100 MHz): δ = 19.9 (q, *C*H$_3$), 52.8 (d, *C*H), 128.7 (d, arom. *C*H), 129.0 (d, arom. *C*H), 133.7 (d, arom. *C*H), 134.1 (s, arom. *C*), 193.6 (s, *C*O).

***d,l*- and *meso*-2,3-Diethyl-1,4-diphenyl-1,4-butandione 3-12b:**



d,l-**3-12b**: R_f = 0.5 (hexane/EtOAc 5:1). - ^{1}H NMR (200 MHz): δ = 0.81 (t, *J* = 7.5 Hz, 6H, CH$_2$C*H*$_3$), 1.69-1.88 (m, 4H, C*H*$_2$CH$_3$), 4.07 (m, 2H, C*H*CH$_2$), 7.36-7.54 (m, 6H, Ph), 7.97 (m, 4H, Ph). - ^{13}C NMR (50 MHz): δ = 10.1 (q, *C*H$_3$), 21.9 (t, *C*H$_2$CH$_3$), 46.5 (d, *C*H), 128.2 (d, Ph), 128.3 (d, Ph), 132.6 (d, Ph), 137.4 (s, Ph), 203.9 (s, *C*O). - MS (+ESI): *m/z* (%) = 611 (3) [3M+Na$^+$], 317 (100) [M+Na$^+$], 295 (13) [M+H$^+$]. - HRMS: $C_{20}H_{23}O_2^+$: calc. 295.1698; found: 295.1693; $C_{20}H_{22}O_2Na^+$: calc. 317.1517; found 317.1512. - Combustion analysis: $C_{20}H_{22}O_2$ (294.39): calc. C 81.60, H 7.53; found C 81.42, H 7.50. - *meso*-**3-12b** detectable resonances: R_f = 0.57 (hexane/EtOAc 5:1). - ^{1}H NMR (200 MHz): δ = 0.69 (t, *J* = 7.4 Hz, 6H, CH$_2$C*H*$_3$), 1.69-1.88 (m, 4H, C*H*$_2$CH$_3$), 3.94 (m, 2H, C*H*CH$_2$), 7.36-7.54 (m, 6H, Ph), 8.07 (m, 4H, Ph). - ^{13}C NMR (50 MHz): δ = 11.5 (q, *C*H$_3$), 25.2 (t, *C*H$_2$CH$_3$), 48.8 (d, *C*H), 128.6 (d, Ph), 138.3 (s, Ph), 203.9 (s, *C*O). - MS (EI): *m/z* (%) = 294 (2) [M$^+$], 276 (10), 261 (3), 189 (3) [M$^+$–PhCO], 161 (6), 148 (25), 105 (100) [PhCO$^+$], 77 (45) [Ph$^+$], 51 (7). - HRMS: $C_{20}H_{22}O_2^+$: calc. 294.1620; found 295.1616.

***meso*- and *d,l-N,N,N',N'*-Tetraethyl-2,3-dipropylsuccindiamide 3-60**

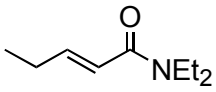


meso-**3-60** *d,l*-**3-60**

d,l-**3-60**: ^{1}H NMR (400 MHz): δ = 0.86 (t, *J* = 7.3 Hz, 6H, CH$_2$CH$_2$C*H*$_3$), 1.00 (t, *J* = 7.0 Hz, 6H, NCH$_2$C*H*$_3$), 1.11 (t, *J* = 7.2 Hz, 6H, NCH$_2$C*H*$_3$), 1.09-1.26 (m, 4H, CH$_2$C*H*$_2$CH$_3$), 1.56 (m, 4H, C*H*$_2$CH), 2.86 (m, 2H, C*H*CONEt$_2$), 3.06-3.20 (m, 4H, NC*H*$_2$), 3.31 (dq, *J* = 13.6, 6.8 Hz, 2H, NC*H*$_2$), 3.59 (dq, *J* = 14.7, 7.3 Hz, 2H, NC*H*$_2$). - ^{13}C NMR (100 MHz): δ = 13.0 (q, *C*H$_3$CH$_2$CH$_2$), 14.4 (q, NCH$_2$*C*H$_3$), 14.6 (q, NCH$_2$*C*H$_3$), 20.6 (t, CH$_2$*C*H$_2$CH$_3$), 33.5 (t, CH*C*H$_2$CH$_2$), 40.3 (t, N*C*H$_2$CH$_3$), 42.2 (t, N*C*H$_2$CH$_3$), 43.8 (d, *C*HCO), 174.2 (s, *C*O). - *meso*-**3-60**: ^{1}H NMR (400 MHz): δ = 0.79 (t, *J* = 7.1 Hz, 6H, CH$_2$CH$_2$C*H*$_3$), 1.11 (t, *J* = 7.0 Hz, 6H,

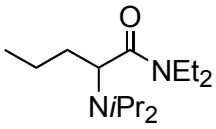
NCH_2CH_3), 1.16 (t, *J* = 7.1 Hz, 6H, NCH_2CH_3), 1.05-1.33 (m, 6H, $CH_2CH_2CH_3$), 1.54 (m, 2H, CH_2CH), 2.95 (m, 2H, $CHCONEt_2$), 3.39 (2xdq, *J* = 14.4, 7.1 Hz, 8H, 4xNCH_2). - ^{13}C NMR (50 MHz): δ = 12.8 (q, $CH_3CH_2CH_2$), 14.3 (q, NCH_2CH_3), 14.7 (q, NCH_2CH_3), 20.9 (t, $CH_2CH_2CH_3$), 34.6 (t, $CHCH_2CH_2$), 40.4 (t, NCH_2CH_3), 42.0 (t, NCH_2CH_3), 44.9 (d, *C*HCO), 174.3 (s, *C*O).

_N,N_-Diethyl-2-pentenoic amide 3-61



Detectable resonances: - ^1H NMR (400 MHz): δ = 2.19 (m, 2H, CH_2CH=), 6.14 (dt, *J* = 15.0, 1.6 Hz, 1H, CH_2CH=), 6.91 (dt, *J* = 15.0, 6.5 Hz, 1H, CH=C*H*CO). - ^{13}C NMR (100 MHz): δ = 12.6 (q, CH_3CH_2CH), 25.5 (t, $CHCH_2CH_3$), 119.5 (d, *C*H=), 147.4 (d, *C*H=).

2-(_N',N'_-Diisopropylamino)-_N,N_-diethylvaleric amide 3-62



^1H NMR (400 MHz): δ = 0.87 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 0.99 (d, *J* = 6.7 Hz, 6H, $NCH(CH_3)_2$), 1.00 (d, *J* = 6.6 Hz, 6H, $NCH(CH_3)_2$), 1.04 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 1.15 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 1.25 (m, 2H, $CH_2CH_2CH_3$), 1.49 (m, 1H, CH_2CH), 1.60 (m, 1H, CH_2CH), 3.10 (dq, *J* = 13.6, 6.8 Hz, 1H, NCH_2), 3.19 (dq, *J* = 14.6, 7.3 Hz, 1H, NCH_2), 3.36 (sept, *J* = 6.6 Hz, 2H, 2x$NCH(CH_3)_2$), 3.48 (m, 1H, NCH_2), 3.51 (t, *J* = 6.9 Hz, 1H, $NCHCH_2$), 3.62 (dq, *J* = 14.5, 7.2 Hz, 1H, NCH_2). - ^{13}C NMR (100 MHz): δ = 12.6 (q, $CH_3CH_2CH_2$), 14.2 (q, NCH_2CH_3), 14.5 (q, NCH_2CH_3), 20.3 (t, $CH_2CH_2CH_3$), 22.9 (q, $NCHCH_3$), 23.3 (q, $NCHCH_3$), 32.6 (t, $CHCH_2CH_2$), 39.9 (t, NCH_2CH_3), 41.2 (t, NCH_2CH_3), 45.4 (d, $NCH(CH_3)_2$), 54.9 (d, *C*HCO), 174.6 (s, *C*O).

Dimerisation of ethyl valerate 3-1a with substoichiometric amounts of TEMPO 1-2

Method A: In five Schlenk flasks five experiments were performed in parallel. BuLi (1.21 mL, 1.6*M* in hexane, 1.95 mmol) was added to a solution of dry *i*Pr_2NH (0.275 mL, 1.95 mmol) in 14 mL dry THF at –78 °C. After stirring at –78 °C for 0.5 h, **3-1a** (195 mg, 1.5 mmol) dissolved in 1 mL of THF was added at –78 °C. The mixture was stirred at –78 °C for 0.5 h, and TEMPO **1-2** (flask1: 23.4 mg, 0.15 mmol; flask 2: 46.8 mg, 0.3 mmol; flask 3: 70.2 mg, 0.45 mmol; flask 4: 93.6 mg, 0.6 mmol; and flask 5: 117 mg, 0.75 mmol) was added as a solid at –78 °C and the mixtures were stirred for 5 min. Ferrocenium hexafluorophosphate **1-3**

was added in small portions at –78 °C consecutively to each of the flasks until a deep blue colour persisted in the reaction mixtures for at least 10 min. The total amounts of **1-3** for 0.15 mmol TEMPO to 0.75 mmol TEMPO were 853 mg, 963 mg, 923 mg, 923 mg and 883 mg, respectively. The progress of the reactions was monitored by TLC (hexane/EtOAc 10:1). The reactions were consecutively quenched with a few drops of water, diluted with diethyl ether, warmed to r.t. and filtered through a pad of silica gel, which was washed with diethyl ether. The solvent was evaporated in vacuo. The inhomogeneous mixtures were preadsorbed on silica gel. Flash chromatography (hexane/ethyl acetate 80:1, gradient to 10:1) afforded ferrocene, followed by a mixture of ferrocene, **3-2a** and *meso*-**3-3a**, a mixture of **3-2a** and *meso*-**3-3a**, and finally a mixture of *meso*-**3-3a** and *d,l*-**3-3a**. For yields and diastereomeric ratios see Table 3.34.

Method B: In five Schlenk flasks five experiments were performed in parallel. Generation of the enolate of **3-1a** (195 mg, 1.5 mmol) in each of the five flasks was performed as in method A.

During deprotonation, 46.8 mg (0.3 mmol), 70.2 mg (0.45 mmol), 93.6 mg (0.6 mmol) or 117 mg (0.75 mmol), respectively, of TEMPO **1-2** was homogeneously mixed with **1-3** (496 mg, 1.5 mmol) in five vials. These mixtures were added in small portions at –78 °C consecutively to each of the reaction mixtures. Subsequently 331 mg of **1-3** was additionally added to each of the flasks and a deep blue colour persisted in the reaction mixtures. The progress of the reactions was monitored by TLC (hexane/EtOAc 10:1). Workup was performed as in method A. For yields and diastereomeric ratios see Table 3.35.

Method C: In five Schlenk flasks five experiments were performed in parallel. Generation of the enolate of **3-1a** (195 mg, 1.5 mmol) in each of the five flasks was performed as in method A.

During deprotonation, 23.4 (0.15 mmol), 46.8 mg (0.3 mmol), 70.2 mg (0.45 mmol) and 93.6 mg (0.6 mmol), respectively, TEMPO was homogeneously mixed with 496 mg (1.5 mmol) of **1-3** in five vials. To each of the flasks 23.4 mg (0.15 mmol) TEMPO was added and these mixtures were stirred for 5 min. The mixtures of **1-2** and **1-3** were added in small portions consecutively to each of the flasks at –78 °C. Subsequently, 100 mg of **1-3** was added to each of the flasks and a deep blue colour persisted in the reaction mixtures. The progress of the reactions was monitored by TLC (hexane/EtOAc 10:1). The workup was performed as in method A. For yields and diastereomeric ratios see Table 3.36.

Dimerisation of the silyl ketene acetal *E*-3-75 (General procedure)

To a solution of ***E*-3-75** (*E:Z* 4:1, 0.362 mL, 1.5 mmol) in 5 mL dry CH_2Cl_2 **1-3** was added in portions at r.t. The first two portions were consumed as it was observed by the disappearance of the deep blue colour. At further addition of **1-3** (total amount 510 mg, 1.54 mmol) the reaction mixture remained dark blue. The reaction mixture was stirred for 10.5 h. The reaction was quenched with a few drops of water, diluted with diethyl ether and filtered through a pad of silica gel. Flash chromatography with hexane/ethyl acetate 80:1, gradient to 5:1 afforded ferrocene (70 mg, 0.38 mmol) followed by 30 mg of *meso*-**3-3a**, 5 mg of a mixture of *meso*-**3-3a** and *d,l*-**3-3a**, and finally 20 mg of *d,l*-**3-3a**. Yield: 28%, d.r. *meso*-**3-3a***:d,l*-**3-3a** 1.3:1.

Dimerisation of *E*-3-75 in the presence of diisopropylamine

To a solution of ***E*-3-75** (*E:Z* 4:1, 304 mg, 1.5 mmol) in 5 mL dry CH_2Cl_2 $i$$Pr_2NH$ (0.423 mL, 3 mmol) was added via syringe at r.t. **1-3** was added in portions. The first two portions were consumed in 5 min for each as it was observed by the disappearance of the deep blue colour. The third portion was consumed in 15 min (total 100 mg). Addition of **1-3** was continued until 580 mg (1.7 mmol) was consumed during 1.5 h. Further 3 mL of solvent and 110 mg of **1-3** was added. After a total oxidation time of 2.5 h, the reaction was quenched with a few drops of water, diluted with diethyl ether and filtered through a pad of silica. Flash chromatography (hexane/ethyl acetate 50:1, gradient to 5:1) afforded ferrocene (110 mg, 0.59 mmol) followed by *meso*-**3-3a** and *d,l*-**3-3a**. Yield: 10% (20 mg), the *meso*-**3-3a***:d,l*-**3-3a** ratio could not be determined from the NMR spectrum.

Dimerisation of the silyl ketene acetal *E*-3-75 after transmetallation with MeLi

To a solution of ***E*-3-75** (*E:Z* 4:1, 210 mg, 1.03 mmol) in 10 mL dry THF MeLi (1.6*M* in Et_2O, 0.643 mL, 1.03 mmol) was added at –30 °C. The reaction was stirred at –30 °C for 5 min and at r.t. for further 90 min. The solution was cooled to –78 °C and **1-3** was added in portions. After addition of 290 mg of oxidant (0.88 mmol), which was consumed in 5 min, the solution turned to dark blue. This colour persisted in the solution for the next 5-10 min, after which another portion of 60 mg of oxidant was added. Stirring was continued at –78 °C for 20 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through a pad of silica gel. The mixture was preadsorbed on silica gel and the solvent was removed in vacuum. Flash chromatography with hexane/ethyl acetate 50:1 gradient to 2:1 afforded a mixture of ferrocene and *meso*-**3-3a**, followed by a mixture of *meso*-**3-3a** and *d,l*-**3-3a**, and finally a mixture of *d,l*-**3-3a** and trimer

3-34a. The yields were determined from the NMR spectra: **3-3a** 74 mg (56%) *meso*:*d,l* 1.8:1; **3-34a** 12 mg (10%). Similar experiments were performed under slightly different conditions. For conditions and yields see Table 3.39, entries 1-8.

Dimerisation of silyl ketene acetal *E*-3-75 after transmetallation with MeLi and in the presence of diisopropylamine

To a solution of ***E*-3-75** (*E:Z* 4:1, 210 mg, 1.03 mmol) in 10 mL dry THF MeLi (1.6*M* in Et_2O, 0.812 mL, 1.3 mmol) was added at –30 °C. The reaction was stirred at –30 °C for 5 min and at r.t. for further 90 min. The solution was cooled to –78 °C and diisopropylamine (0.183 mL, 1.3 mmol) was added via syringe. **1-3** was added in portions (total amount 320 mg, 0.97 mmol) at –78 °C over 15 min until a dark blue colour persised in the solution for at least 10 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through a pad of silica gel. The mixture was preadsorbed on silica gel and the solvent was removed in vacuum. Flash chromatography with hexane/ethyl acetate 100:1, gradient to 2:1 afforded ferrocene (160 mg, 0.86 mmol), followed by *meso*-**3-3a**, a mixture of *meso*-**3-3a** and *d,l*-**3-3a**, and finally a mixture of *d,l*-**3-3a** and trimer **3-34a**. The yields were determined from the NMR spectra: **3-3a** 75 mg (58%) *meso*:*d,l* 3.2:1; **3-34a** 34 mg (20%). This experiment was repeated. The yields were reproducible, while the diastereoselectivities were very different. For yields see Table 3.39, entries 9-11.

Dimerisation of silyl ketene acetal *E*-3-75 after transmetallation with MeLi in the presence of TEMPO

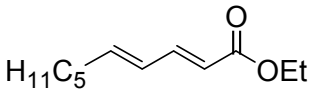
To a solution of ***E*-3-75** (*E:Z* 4.5:1, 210 mg, 1.03 mmol) in 10 mL dry THF MeLi (1.6*M* in Et_2O, 0.812 mL, 1.3 mmol) was added at –30 °C. The reaction was stirred at –30 °C for 5 min and at r.t. for further 90 min. The solution was cooled to –78 °C and TEMPO (47 mg, 0.3 mmol) was added and the solution was stirred for 5 min. Ferrocenium hexafluorophosphate was added in portions (total amount 350 mg, 1.06 mmol) at –78 °C over 15 min until a dark blue colour persised in the solution for at least 10 min. The reaction was quenched with a few drops of water, diluted with diethyl ether and warmed to r.t. The reaction mixture was filtered through a pad of silica gel. Flash chromatography (hexane/ethyl acetate 80:1 gradient to 2:1) afforded ferrocene, followed by a mixture of ferrocene, TEMPO trapping product **3-2a** and *meso*-**3-3a**, a mixture of TEMPO trapping product **3-2a** and *meso*-**3-3a**, and finally a mixture of *d,l*-**3-3a** and trimer **3-34a**. Further purification was necessary. The yields were determined

from the NMR spectra: 77 mg (27%) **3-2a**, 20 mg (15%) *meso*:*d,l* 4.6:1 **3-3a**; 36 mg (32%) **3-34a**. This experiment was repeated. The results were not well reproducible. For yields and conditions see Table 3.39, entries 12-14.

6.9. Total syntheses of 15-F_{2t}-isoprostane, 13,14-dihydro-15-oxo-15-E_2-isoprostane and 13,14-dihydro-15-oxo-15-prostaglandin-E_2

6.9.1 Substrate Synthesis

***(2E,4E)*-Ethyl 2,4-decadienoate *(2E,4E)*-4-14**[172a,b,d]

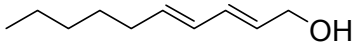


A solution of 15 g (76.4 mmol) of *(2E,4Z)*-ethyl 2,4-decadienoate[172c,d] *(2E,4Z)*-**4-13** and 0.83 g (5 mol%) Ph_2S_2 in 225 mL benzene was irradiated with UV light of a 150 W quartz lamp under a nitrogen atmosphere for 3 h. The solvent was evaporated and the crude mixture was dried in high vacuum for 20 min. Distillation at 0.9 mbar gave 12.05 g pure ester, bp 83-93 °C/0.9 mbar. The brown residue (5.3 g) was purified by flash chromatography (hexane/ethyl acetate 20:1 gradient 10:1) to give 1.2 g of the pure ester contaminated with 0.75 g of Ph_2S_2. Yield 88% yield (13.25 g), *(2E,4E):(2E,4Z)* 8.3:1.

A second isomerisation with 15 g of *(2E,4Z)*-**4-13** gave 11.8 g (79% yield) *(2E,4E):(2E,4Z)* 8.3:1. The distillation gave 10.4 g of pure ester, but longer heating at higher temperatures (up to 140 °C) led to decomposition. Column chromatography of the distillation residue with hexane/ethyl acetate 20:1 gave 2.07 g containing 1.47 g ester and 0.59 g of Ph_2S_2. The presence of Ph_2S_2 did not disturb the reduction to *(2E,4E)*-**4-15** and its purification.

R_f (hexane/ethyl acetate 20:1) = 0.34. - bp 90-93 °C/0.9 mbar. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3H, $CH_2CH_2CH_3$), 1.22-1.50 (m, 9H, $CH_2CH_2CH_2CH_3$, OCH_2CH_3), 2.15 (m, 2H, CH_2CH=), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 5.78 (d, *J* = 15.3 Hz, 1H, CH=$CHCO_2Et$), 6.14 (m, 2H, CH_2CH=CH), 7.25 (dd, *J* = 10.1, 15.4 Hz, 1H, CH=$CHCO_2Et$). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (q, OCH_2CH_3), 14.3 (q, CH_2CH_3), 22.4 (t, CH_2CH_3), 28.4 (t, $CH_2CH_2CH_2CH_3$), 31.3 (t, $CH_2CH_2CH_2CH_3$), 32.9 (t, CH_2CH=), 60.1 (t, OCH_2CH_3), 119.1 (d, =$CHCO_2Et$), 128.3 (d, =$CHCH$=$CHCO_2Et$), 144.7 (d, CH_2CH=), 145.1 (d, CH=$CHCO_2R$), 167.3 (s, CO_2Et).

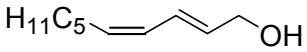
***(2E,4E)*-Deca-2,4-dien-1-ol *(2E,4E)*-4-15**



To a solution of *(2E,4E)*-**4-14** (11.87 g, 60.6 mmol) and residual of Ph_2S_2 (0.59 g, 2.7 mmol) in 250 mL CH_2Cl_2 DIBAL-H (160 mL = 63 mL 1*M* in CH_2Cl_2 + 97 mL 1*M* in hexane, 160 mmol) was added dropwise with a dropping funnel over 55 min at −78 °C. The reaction was monitored by TLC from a hydrolysed sample. After 1 h of stirring at −78 °C, the reaction was complete. It was quenched very slowly with 40 mL of saturated NH_4Cl solution at −78 °C and warmed to r.t. The white suspension was dissolved by careful addition of 100 mL 2*M* solution of H_2SO_4 with stirring. The aqueous layer was extracted with diethyl ether (4x30 mL). The combined organic layers were washed twice with water, twice with $NaHCO_3$ and twice with brine. Drying over Na_2SO_4 and concentration gave the crude product (10.15 g), which was purified by flash chromatography with hexane/ethyl acetate 20:1 gradient to 2:1 (the product eluted at 5:1). Colourless oil, yield 8.73 g (94%), *(2E,4E):(2E,4Z)* 14:1. A repetition afforded the product in 79% yield and ratio of *(2E,4E):(2E,4Z)* 6:1.

R_f (hexane/ethyl acetate 5:1) = 0.25 - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 1.23-1.47 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.59 (br. s, 1H, O*H*), 2.07 (q, *J* = 6.9 Hz, 2H, $CH_2CH_2CH_2CH_2CH_3$), 4.17 (d, *J* = 6.0 Hz, 2H, CH_2OH), 5.71 (m, 2H, C*H*=CHCH=C*H*), 6.04 (dd, *J* = 15.2, 10.5 Hz, 1H, $CHCH=CHCH_2OH$), 6.21 (dd, *J* = 15.1, 10.4 Hz, 1H, C*H*=$CHCH_2OH$). - ^{13}C NMR (75 MHz): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 28.9 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_2CH_3$), 32.6 (t, CH_2CH=), 63.5 (t, CH_2OH), 129.3 (d, =$CHCH$=$CHCH_2OH$), 132.1 (d, =$CHCH_2OH$), 135.8 (d, CH_2CH_2CH=).

***(2E,4Z)*-Deca-2,4-dien-1-ol *(2E,4Z)*-4-15**



To a solution of *(2E,4Z)*-**4-13** (5.0 g, 26 mmol) in 120 mL dry THF was added $LiAlH_4$ (1.03 g, 27 mmol) at 0 °C under a N_2 atmosphere, carefully in small portions. The reaction was monitored by TLC and was quenched after completion carefully dropwise with water at the same temperature. The white aluminium salts were dissolved by careful addition of a 10% H_2SO_4 solution. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed three times with $NaHCO_3$ solution and brine. They were dried over $NaSO_4$ and the solvent was removed in vacuum. The crude product (4.8 g) was purified by flash chromatography with hexane/ethyl acetate 20:1, gradient to 5:1. Yield 2.8 g (71%) as a colourless oil.

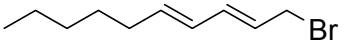
R_f (hexane/ethyl acetate 5:1) = 0.23 - ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 3H, CH_2CH_3), 1.24-1.45 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.73 (br. s, 1H, O*H*), 2.14 (q, *J* = 7.2 Hz, 2H, $=CHCH_2CH_2$), 4.19 (d, *J* = 5.9 Hz, 2H, CH_2OH), 5.46 (m, 1H, CH_2CH_2CH), 5.80 (dt, *J* = 15.1, 5.9 Hz, 1H, $CHCH_2OH$), 5.99 (t, *J* = 10.9 Hz, 1H, $CHCH=CHCH_2OH$), 6.53 (ddt, *J* = 15.3, 11.1, 1.3 Hz, 1H, $CH=CHCH_2OH$). - ^{13}C NMR (50 MHz): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 27.7 (t, $CH_2CH_2CH_2CH_3$), 29.3 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH=$), 63.5 (t, CH_2OH), 126.8 (d, $CHCH=CHCH_2OH$), 127.5 (d, $CHCH=CHCH_2OH$), 131.5 (d, $=CHCH_2OH$), 133.2 (d, $CH_2CH_2CH=$).

***(2E,4Z)- and (2E,4E)*-Bromodeca-2,4-diene 4-16 and *(3E)*-5-bromodeca-1,3-diene *(3E)*-4-17**

Method A: A solution of PBr_3 (0.99 mL, 10.5 mmol) dissolved in 5 mL diethyl ether was added with a dropping funnel to a solution of *(2E,4E)*-**4-15** (4.77 g, 31 mmol) in 30 mL dry diethyl ether at −20 °C over 30 min. The reaction was stirred at −15 °C for 1.5 h. Since the TLC didn't change anymore, PBr_3 (0.3 mL, 3.2 mmol) was added via syringe to the reaction mixture and it was warmed to 0 °C for 30 min. The spot on TLC having the same R_f as the alcohol did not disappear, but was not UV active. The reaction was quenched very carefully with 70 mL saturated $NaHCO_3$ solution. The aqueous phase was extracted three times with diethyl ether. The combined ethereal phases were washed with water and brine, dried over Na_2SO_4, concentrated and dried in high vacuum. The crude 3.8:1 mixture of *(2E,4E)*-**4-16** and *(3E)*-**4-17** (6.06 g) was employed without further purification in the subsequent alkylation.

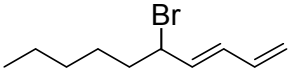
Method B: A solution of PBr_3 (0.73 mL, 7.8 mmol) dissolved in 5 mL CH_2Cl_2 was added with a dropping funnel to a solution of *(2E,4E)*-**4-15** (3.5 g, 23 mmol) in 13 mL dry CH_2Cl_2 at −20 °C over 15 min. The reaction was stirred at −10 °C for 0.5 h, when it was complete by TLC (hexane/ethyl acetate 5:1). The reaction mixture was carefully quenched with 20 mL saturated $NaHCO_3$ solution. The aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude 1.7:1 mixture (4.5 g) of *(2E,4E)*-**4-16** and *(3E)*-**4-17** was purified on a short column with hexane/ethyl acetate 30:1, gradient to 5:1. Yield 3.33 g (67%) of *(2E,4E)*-**4-16:***(3E)*-**4-17** as a 8.7:1 mixture at 30:1-20:1 followed by 0.64 g (18%) of *(3E)*-**4-18** at 10:1.

(2*E*,4*E*)-1-Bromodeca-2,4-diene (2*E*,4*E*)-4-16



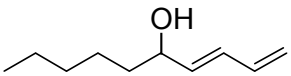
R_f(hexane/ethyl acetate 5:1) = 0.24. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.29 (m, 4H, $CH_2CH_2CH_3$), 1.38 (m, 2H, CH_2CH_2CH=), 2.09 (q, *J* = 7.0 Hz, 2H, CH_2CH=), 4.03 (d, *J* = 8.0 Hz, 2H, CH_2Br), 5.76 (m, 2H, C*H*=CHCH=C*H*CH_2Br), 6.03 (dd, *J* = 15.1, 10.7 Hz, 1H, C*H*=CHCH_2Br or =C*H*CH=CHCH_2Br), 6.26 (dd, *J* = 15.1, 10.8 Hz, 1H, C*H*=CHCH_2Br or =C*H*CH=CHCH_2Br). - ^{13}C NMR (75 MHz): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 28.7 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_3$), 32.6 (t, $CH_2CH_2CH_2CH_2CH_3$), 33.8 (t, CH_2Br), 126.1 (d, =CHCH$_2$Br or CH_2CH_2CH=), 128.7 (d, =CHCH=CHCH_2Br or CH=CHCH_2Br), 135.4 (d, =CHCH=CHCH_2Br or CH=CHCH_2Br), 137.8 (d, =CHCH_2Br or CH_2CH_2CH=).

(3*E*)-5-Bromodeca-1,3-diene (3*E*)-4-17



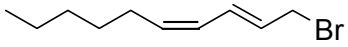
R_f (hexane/ethyl acetate 5:1) = 0.24 - Detectable resonances: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.25-1.42 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.90 (m, 2H, CH_2CHBr), 4.57 (dt, *J* = 9.5, 7.1 Hz, 2H, C*H*Br), 5.15 (dd, *J* = 11.1, 1.5 Hz, 1H, CH_2=CH), 5.26 (d, *J* = 16.3 Hz, 1H, CH_2=CH), 5.85 (dd, *J* = 15.0, 9.1 Hz, 1H, =C*H*CHBr), 6.19 (m, 1H, =C*H*CH=CH_2), 6.32 (m, 1H, C*H*=CH_2). - ^{13}C NMR (100 MHz): δ = 39.1 (t, CH_2CHBr), 55.9 (d, CHBr), 119.0 (t, CH_2=CH), 132.2 (d, BrCHCH=CH), 134.7 (d, =CHCHBr), 135.6 (d, CH=CH_2).

(3*E*)-Deca-1,3-dien-5-ol (3*E*)-4-18



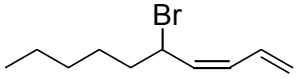
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (m, 3H, CH_2CH_3), 1.29-1.47 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.52 (m, 2H, CH_2CHOH), 4.12 (m, 1H, CHOH), 5.06 (d, *J* = 9.8 Hz, 1H, CH_2=CH), 5.18 (d, *J* = 16.6 Hz, 1H, CH_2=CH), 5.71 (dd, *J* = 15.0, 6.6 Hz, 1H, CH=CHCHOH), 6.20 (m, 1H, CH_2=CHCH), 6.32 (m, 1H, CH_2=CH). - ^{13}C NMR (100 MHz): δ = 13.8 (q, CH_2CH_3), 22.4 (t, CH_2CH_3), 24.9 (t, $CH_2CH_2CH_2CH_3$), 31.6 (t, $CH_2CH_2CH_3$), 37.1 (t, CH_2CHOH), 72.1 (t, CHOH), 116.9 (t, CH_2=CH), 130.5 (d, CH=CHCHOH), 136.3 (d, CH_2=CH), 136.8 (d, =CHCHOH).

(2*E*,4*Z*)-1-Bromodeca-2,4-diene (2*E*,4*Z*)-4-16



R_f (hexane/ethyl acetate 5:1) = 0.24. - ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 3H, CH_2CH_3), 1.21-1.46 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.15 (dq, *J* = 7.3, 1.1 Hz, 2H, CH_2CH=), 4.06 (dd, *J* = 7.8, 0.7 Hz, 2H, CH_2Br), 5.52 (dt, *J* = 10.8, 7.7 Hz, 1H, C*H*=), 5.86 (m, 2H, C*H*=), 6.58 (m, 1H, C*H*=). - ^{13}C NMR (50 MHz): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 27.8 (t, $CH_2CH_2CH_2CH_3$), 29.2 (t, $CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_2CH_2CH_3$), 33.6 (t, CH_2Br), 126.9 (d, *C*H=), 128.1 (d, *C*H=), 130.2 (d, *C*H=), 135.1 (d, *C*H=).

***(3Z)*-5-Bromodeca-1,3-diene *(3Z)*-4-17**



R_f (hexane/ethyl acetate 5:1) = 0.24. - Detectable resonances ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (m, 3H, CH_2CH_3), 1.21-1.46 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.74-2.07 (m, 2H, CH_2CHBr), 4.57 (dt, *J* = 9.5, 7.1 Hz, 1H, C*H*Br), 5.15 (m, 1H, CH_2=CH), 5.26 (m, 1H, CH_2=CH), 5.80 (m, 1H, C*H*CHBr), 6.25 (m, 2H, $CHCH$=CH_2). - ^{13}C NMR (50 MHz): δ = 13.9 (q, CH_2CH_3), 22.4 (t, CH_2CH_3), 27.4 (t, $CH_2CH_2CH_2CH_3$), 31.1 (t, $CH_2CH_2CH_3$), 39.1 (t, CH_2CHBr), 55.8 (d, *C*HBr), 119.0 (t, CH_2=CH), 132.2 (d, BrCHCH=*C*H), 134.6 (d, =*C*HCHBr), 135.6 (d, CH_2=*C*H).

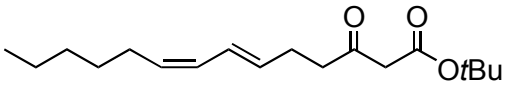
***(6E,8E)*- or *(6E,8Z)-tert*-Butyl or methyl 3-oxotetradeca-6,8-dienoates 4-20a,b**

Method A with crude **4-16**/**4-17**: *tert*-Butyl acetoacetate **4-19b** (7.34 mL, 45 mmol) diluted with 5 mL dry THF was added dropwise to a suspension of NaH (2.16 g, 54 mmol, 60% in mineral oil) in 100 mL dry THF at 0 °C. After stirring for 15 min the reaction was cooled to −50 °C and BuLi (31 mL, 49.5 mmol, 1.6*M* in hexane) was added. The reaction was stirred at this temperature for 30 min during which it became white inhomogeneous. The crude 3.8:1 mixture of bromides *(2E,4E)*-**4-16** and *(3E)*-**4-17** (6.06 g, 29 mmol) diluted with dry THF was added at 0 °C. The reaction was stirred at this temperature until complete as indicated by TLC (1 h). It was quenched with a 10% HCl solution (20 mL). The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with water, $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated in vacuum. The crude mixture (12 g) was purified by flash chromatography (hexane/ethyl acetate 20:1 gradient to 2:1). The products eluted in the following order: A complex mixture of **4-19b** and byproduct

(3E)-**4-21b**, followed by *(6E,8E)*-**4-20b** containing traces of *(3E)*-**4-21b.** Yield 3.4 g (37%) based on the dienol *(2E,4E)*-**4-15** as colourless oil.

Method B with purified **4-16**/**4-17**: A solution of methyl acetoacetate **4-19a** (2.23 g, 19.2 mmol) in 7 mL dry THF was added dropwise to a suspension of NaH (0.92 g, 23 mmol, 60% in mineral oil) in 25 mL dry THF at 0 °C. After stirring for 0.5 h, BuLi (13.2 mL, 21.1 mmol, 1.6*M* solution in hexane) was added at –60 °C. The reaction mixture was stirred at –60 °C for 15 min and at 0 °C for 15 min. The 8.7:1 mixture of *(2E,4E)*-**4-16** and *(3E)*-**4-17** (3.33 g, 15.3 mmol) dissolved in 8 mL dry THF was added at 0 °C. The deep yellow colour changed to pale yellow and the reaction became inhomogeneous. The reaction was stirred at 0 °C for 1 h and at r.t. for 30 min. It was quenched with a 10% HCl solution. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated in vacuum. The crude mixture (4.16 g) was purified by flash chromatography (hexane/ethyl acetate 30:1 gradient to 10:1). The products eluted starting with 20:1 in the following order: 2.14 g of a 16:1 mixture of *(6E,8E)*-**4-20a** and *(6E)*-**4-21a**, followed by 0.32 g of a 8.8:1 mixture of *(6E,8E)*-**4-20a** and *(6E)*-**4-21a.** Yield 2.3 g (40%) based on the dienol *(2E,4E)*-**4-15** as a colourless oil**.** Byproduct **4-21a** was separated by a second column or by purification in the next step.

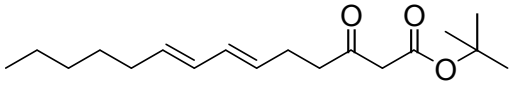
(6*E*,8*Z*)-*tert*-Butyl 3-oxotetradeca-6,8-dienoate (6*E*,8*Z*)-4-20b



IR: $\tilde{\nu}$ = 2957 (m), 2930 (m), 2861 (s), 1712 (s), 1642 (w), 1457 (w), 1367 (m), 1318 (m), 1251 (m), 1146 (s), 967 (m), 840 (w), 730 (w). - MS (EI) *m/z* (%): 294 (3.8) [M^+], 238 (18) [M^+–$H_2CC(CH_3)_2$], 221 (8) [M^+–$OC(CH_3)_3$], 178 (12) [M^+–$CH_3COOC(CH_3)_3$], 136 (61) [M^+– $CH_3COCH_2COOC(CH_3)_3$], 95 (22), 79 (57), 67 (35), 57 (100) [$(CH_2)_3CH_3^+$ or tBu$^+$], 43 (34) [$(CH_2)_2CH_3^+$]. - Combustion analysis: $C_{18}H_{30}O_3$ (294.43): calc. C 73.43, H 10.27; found C 73.09, H 10.42. - R_f (hexane/ethyl acetate 5:1) = 0.60, R_f (hexane/ethyl acetate 10:1) = 0.34. - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.23-1.41 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.43 (s, 9H, $C(CH_3)_3$), 2.10 (m, 2H, =$CHCH_2$), 2.35 (q, *J* = 7.3 Hz, 2H, CH_2CH_2CO), 2.60 (t, *J* = 7.4 Hz, 2H, CH_2CH_2CO), 3.30 (s, 2H, CH_2COO*t*Bu), 5.29 (dt, *J* = 10.8, 7.6 Hz, 1H, =$CH(CH_2)_3$), 5.57 (dt, *J* = 15.1, 7.3 Hz, 1H, =$CHCH_2CH_2CO$), 5.87 (t, *J* = 10.9 Hz, 1 H, CH=$CH(CH_2)_3$), 6.29 (ddd, *J* = 15.1, 10.9, 1.3 Hz, 1H, CH=$CHCH_2CH_2CO$). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 26.6 (t, CH_2CH_2CO), 27.6 (t, $CH_2CH_2CH_2CH_2CH_3$), 27.9 (q, $C(CH_3)_3$), 29.3 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_3$), 42.4 (t, CH_2CH_2CO), 50.6 (t, CH_2COO*t*Bu), 81.9 (s, $C(CH_3)_3$), 126.7 (d,

*C*H=CHCH$_2$CH$_2$CO), 128.1 (d, (CH$_2$)$_3$CH=*C*H) 131.1 (d, CH$_3$(CH$_2$)$_4$*C*H), 131.6 (d, *C*H(CH$_2$)$_2$CO), 166.3 (s, CH$_2$*C*O*O*t*Bu), 202.3 (s, CH$_2$*C*OCH$_2$). - Detectable resonances of the enol form: ^{1}H NMR (400 MHz): δ = 1.45 (s, 9H, C(C*H*$_3$)$_3$), 4.86 (s, 1H, =C*H*COO*t*Bu). - ^{13}C NMR (100 MHz): δ = 90.6 (d, =*C*HCOO*t*Bu).

(6*E*,8*E*)-*tert*-Butyl 3-oxotetradeca-6,8-dienoate (6*E*,8*E*)-4-20b

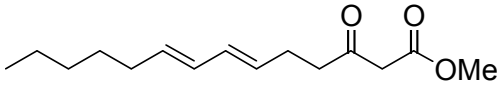


R_f (hexane/ethylacetate 10:1) = 0.27. - ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3H, CH$_2$C*H*$_3$), 1.20-1.45 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.47 (s, 9H, C(C*H*$_3$)$_3$), 2.04 (q, *J* = 6.8 Hz, 2H, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.35 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_2$C=O), 2.62 (m, 2H, CH$_2$C*H*$_2$C=OCH$_2$), 3.34 (s, 2H, C*H*$_2$COO*t*Bu), 5.57 (m, 2H, C*H*=CHCH=C*H*CH$_2$), 5.97 (m, 2H, CH=C*H*C*H*=CHCH$_2$). - ^{13}C NMR (50 MHz, CDCl$_3$): δ = 13.9 (q, CH$_2$*C*H$_3$), 21.4 (t, *C*H$_2$CH$_3$), 26.3 (t, *C*H$_2$CH$_2$C=O), 27.9 (q, C(*C*H$_3$)$_3$), 28.9 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.3 (t, *C*H$_2$CH$_2$CH$_3$), 32.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 42.4 (t, *C*H$_2$C=O), 50.6 (t, O=C*C*H$_2$COOR), 81.8 (s, *C*(CH$_3$)$_3$), 129.3 (d, *C*HCH$_2$CH$_2$CO), 129.8 (d, (CH$_2$)$_3$CH=*C*H) 131.5 (d, *C*H=CH(CH$_2$)$_2$CO), 133.5 (d, CH$_3$(CH$_2$)$_4$*C*H), 166.3 (s, CH$_2$*C*O*O*t*Bu), 202.4 (s, CH$_2$*C*OCH$_2$). - Detectable resonances of the enol form: ^{1}H NMR (200 MHz): δ = 4.88 (s, 1H, =C*H*COOMe). - ^{13}C NMR (50 MHz): δ = 89.8 (d, =*C*HCOOMe).

Methyl 3-oxotetradeca-6,8-dienoates *(6E,8E)*-4-20a and *(6E,8Z)*-4-20a

IR (Film): $\tilde{\nu}$ = 3019 (br. w), 2956 (w), 2926 (m), 2856 (w), 1747 (s), 1717 (s), 1653 (w), 1629 (w), 1437 (m), 1407 (w), 1318 (m), 1237 (m), 1194 (w), 1153 (m), 986 (m), 949 (w), 844 (w), 734 (w). - MS (EI) *m/z* (%): 252 (10) [M$^+$], 234 (15) [M$^+$–H$_2$O], 220 (5) [M$^+$–CH$_3$OH], 178 (11) [M$^+$–CH$_3$COOCH$_3$], 150 (19) [M$^+$–COCH$_2$COOMe·-H·], 136 (56) [M$^+$–CH$_3$COCH$_2$COOCH$_3$], 101 (24) [COCH$_2$COOMe$^+$·], 93 (35) [M$^+$–CH$_3$COCH$_2$COOCH$_3$–C$_3$H$_7$$^+$·], 91 (24), 79 (100) [M$^+$– CH$_3$COCH$_2$COOCH$_3$-C$_4H_9$$^+$·], 67 (53), 59 (21) [COOMe$^+$·], 55 (15). - Combustion analysis: C$_{15}$H$_{24}$O$_3$ (252.35): calc. C 71.39, H 9.59; found C 70.98, H 9.95.

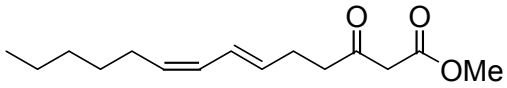
***(6E,8E)*-Methyl 3-oxotetradeca-6,8-dienoate *(6E,8E)*-4-20a**



R_f (hexane/ethyl acetate 5:1) = 0.47. - ^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH$_2$C*H*$_3$), 1.29 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.37 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.04 (q, *J* = 7.2 Hz, 2H,

C*H*$_2$(CH$_2$)$_3$CH$_3$), 2.33 (m, 2H, C*H*$_2$CH$_2$CO), 2.64 (q, *J* = 7.4 Hz, 2H, CH$_2$C*H*$_2$CO), 3.446 (s, 2H, C*H*$_2$COOMe), 3.724 (s, 3H, COOC*H*$_3$), 5.51 (dt, *J* = 14.0, 6.9 Hz, =C*H*(CH$_2$)$_2$CO), 5.60 (m, 1H, (CH$_2$)$_3$C*H*=CH), 6.10 (m, 2H, (CH$_2$)$_3$CH=C*H*C*H*). - ^{13}C NMR (100 MHz): δ = 13.8 (q, CH$_2$*C*H$_3$), 22.4 (t, *C*H$_2$CH$_3$), 26.2 (t, *C*H$_2$CH$_2$CO), 28.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.2 (t, *C*H$_2$CH$_2$CH$_3$), 32.4 (t, CH$_2$CH$_2$*C*H$_2$CH=), 42.4 (t, CH$_2$*C*H$_2$CO), 48.8 (t, *C*H$_2$COOR), 52.1 (q, COO*C*H$_3$), 129.0 (d, =*C*HCH$_2$CH$_2$CO), 129.7 (d, (CH$_2$)$_3$CH=*C*H), 131.5 (d, *C*H=CH(CH$_2$)$_2$CO), 133.4 (d, CH$_3$(CH$_2$)$_4$*C*H=), 167.5 (s, CH$_2$*C*OOMe), 201.7 (s, CH$_2$*C*OCH$_2$). - Detectable resonances of the enol: ^{1}H NMR (400 MHz): δ = 4.99 (s, 1H, =C*H*COOMe). - ^{13}C NMR (100 MHz): δ = 93.8 (d, =*C*HCOOMe).

***(6E,8Z)*-Methyl 3-oxotetradeca-6,8-dienoate *(6E,8Z)*-4-20a**



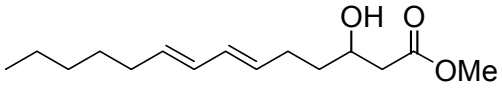
R$_f$ (hexane/ethyl acetate 5:1) = 0.5. - ^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH$_2$C*H*$_3$), 1.29 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.37 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.14 (q, *J* = 7.3 Hz, 2H, C*H*$_2$(CH$_2$)$_3$CH$_3$), 2.39 (q, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_2$CO), 2.64 (q, *J* = 7.4 Hz, 2H, CH$_2$C*H*$_2$CO), 3.45 (s, 2H, C*H*$_2$COOMe), 3.722 (s, 3H, COOC*H*$_3$), 5.33 (dt, *J* = 10.6, 7.6 Hz, 1H, (CH$_2$)$_3$C*H*=CH), 5.60 (dt, *J* = 14.1, 6.7 Hz, 1H, =C*H*(CH$_2$)$_2$CO), 5.91 (t, *J* = 10.9 Hz, 1H, (CH$_2$)$_3$CH=C*H*), 6.33 (dd, *J* = 15.0, 10.9 Hz, 1H, C*H*=CHCH$_2$CH$_2$CO). - ^{13}C NMR (100 MHz): δ = 13.8 (q, CH$_2$*C*H$_3$), 22.4 (t, *C*H$_2$CH$_3$), 26.5 (t, *C*H$_2$CH$_2$CO), 27.5 (t, CH$_2$CH$_2$*C*H$_2$CH=) 29.2 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.3 (t, *C*H$_2$CH$_2$CH$_3$), 42.4 (t, CH$_2$*C*H$_2$CO), 48.8 (t, *C*H$_2$COOR), 52.1 (q, COO*C*H$_3$), 126.7 (d, *C*H=CH(CH$_2$)$_2$CO), 127.9 (d, (CH$_2$)$_3$CH=*C*H), 131.0 (d, CH$_3$(CH$_2$)$_4$*C*H=), 131.3 (d, =*C*HCH$_2$CH$_2$CO), 167.3 (s, CH$_2$*C*OOMe), 201.6 (s, CH$_2$*C*OCH$_2$). - Detectable resonances of the enol: ^{1}H NMR (400 MHz): δ = 5.00 (s, 1H, =C*H*COOMe). - ^{13}C NMR (100 MHz): δ = 88.9 (d, =*C*HCOOMe).

***(6E,8E)*- and *(6E,8Z)*-3-Hydroxytetradeca-6,8-dienoates 4-11a**

A solution of *(6E,8E)*-**4-20a** (2.23 g, 8.85 mmol) was added dropwise to a suspension of NaBH$_4$ (403.6 mg, 10.62 mmol) in 30 mL dry MeOH at 0 °C, with strong stirring. The reaction was monitored by TLC (hexane/EtOAc 2:1). The reaction mixture was carefully quenched with 10 mL of NaHCO$_3$ solution. The methanol was evaporated and the remaining aqueous layer was extracted three times with diethyl ether. The combined ethereal layers were dried over NaSO$_4$ and concentrated in vacuum. Column chromatography (hexane/EtOAc 5:1 gradient to 2:1) afforded 1.86 g (83%) *(6E,8E)*-**4-11a** as a colourless oil.

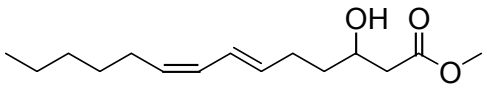
***(6E,8E)*-4-11a** and ***(6E,8Z)*-4-11a**: IR (ATR): $\tilde{\nu}$ = 3462 (w), 3018 (w), 2955 (m), 2925 (s), 2856 (w), 1726 (s), 1438 (s), 1410 (w), 1356 (w), 1288 (w), 1252 (w), 1197 (m), 1160 (s), 1084 (w), 1061 (w), 984 (s), 948 (m), 842 (w), 728 (w), 605 (w) cm^{-1}. - MS (EI): *m/z* (%) = 254 (3) [M^+], 236 (18) [M^+–H_2O], 162 (18), 152 (15), 147 (28), 135 (9), 133 (17), 129 (13), 119 (32), 105 (71), 97 (28) [$C_5H_{11}CH{=}CH$], 95 (39), 91 (54), 81 (60), 79 (59), 71 (41) [C_5H_{11}], 67 (100), 57 (68), 55 (73), 53 (19), 51 (13). - Combustion analysis: $C_{15}H_{26}O_3$ (254.36): calc. C 70.83, H 10.30; found C 70.46, H 10.47.

***(6E,8E)*-Methyl 3-hydroxytetradeca-6,8-dienoate *(6E,8E)*-4-11a**



R_f (hexane/ethyl acetate 5:1) = 0.25 - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 1.22-1.42 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.51 (m, 1H, CH_2CH_2CHOH), 1.62 (m, 1H, CH_2CH_2CHOH), 2.04 (q, *J* = 7.2 Hz, 2H, $=CHCH_2CH_2CH_2$), 2.20 (m, 2H, CH_2CH_2CHOH), 2.46 (AB part of ABX system, *J* = 16.3, 8.6, 3.8 Hz, 2H, CH_2COOMe), 3.11 (s, O*H*), 3.70 (s, 3H, $COOCH_3$), 4.01 (m, 1H, C*H*OH), 5.56 (m, 2H, $CH{=}CHCH{=}CHCH_2$), 6.01 (m, 2H, $=CHCH{=}CHCH_2$) - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (q, CH_2CH_3), 22.4 (t, CH_2CH_3), 28.4 (t, CH_2CH_2CHOH), 28.9 (t, $CH_2CH_2CH_2CH_3$), 31.3 (t, $CH_3CH_2CH_2$), 32.4 (t, $CH_2CH_2CH_2CH{=}$), 36.0 (t, CH_2CH_2CHOH), 41.1 (t, CH_2COOMe), 51.5 (d, $COOCH_3$), 67.2 (d, *C*HOH), 130.0 (d, $CH{=}CH(CH_2)_3$), 130.7 (d, $CH{=}CH(CH_2)_2CHOH$ or $=CH(CH_2)_2CHOH$), 131.0 (d, $CH{=}CH(CH_2)_2CHOH$ or $=CH(CH_2)_2CHOH$), 132.9 (d, $=CH(CH_2)_3$), 173.1 (s, *C*OO).

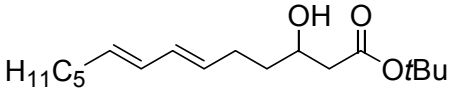
***(6E,8Z)*-Methyl 3-hydroxytetradeca-6,8-dienoate *(6E,8Z)*-4-11a**



R_f (hexane/ethyl acetate 2:1) = 0.63 - ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.5 Hz, 3H, CH_2CH_3), 1.22-1.37 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.57 (m, 2H, CH_2CH_2CHOH), 2.18 (m, 4H, $=CHCH_2CH_2CH_2CH_2$, CH_2CH_2CHOH), 2.48 (AB part of ABX system, *J* = 16.3, 8.0, 4.2 Hz, 2H, CH_2COOMe), 3.71 (s, 3H, $COOCH_3$), 4.02 (m, 1H, C*H*OH), 5.32 (dt, *J* = 10.8, 7.6 Hz, 1H, $(CH_2)_4CH{=}$), 5.64 (dt, *J* = 15.0, 7.0 Hz, 1H, $=CHCH_2CH_2CHOH$), 5.93 (t, *J* = 10.9 Hz, 1H, $(CH_2)_4CH{=}CH$), 6.35 (ddd, *J* = 15.0, 10.9, 1.1 Hz, 1H, $CH{=}CHCH_2CH_2CHOH$). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 27.6 (t,

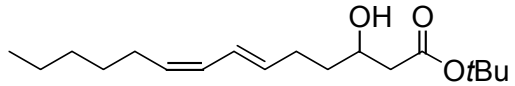
CH_2CH_2CHOH), 28.7 (t, *C*$H_2CH_2CH_2CH_3$), 29.3 (t, $CH_3CH_2CH_2$), 31.4 (t, $CH_2CH_2CH_2CH$=), 36.0 (t, CH_2CH_2CHOH), 41.1 (t, *C*H_2COOMe), 51.7 (d, $COOCH_3$), 67.4 (d, *C*HOH), 126.3 (d, *C*H=$CHCH_2CH_2CHOH$), 128.2 (d, *C*H=$CH(CH_2)_4$), 130.6 (d, =*C*H$(CH_2)_4$), 133.0 (d, =*C*HCH_2CH_2CHOH), 173.2 (s, *C*OO).

***(6E,8E)-tert*-Butyl 3-hydroxytetradeca-6,8-dienoate *(6E,8E)*-4-11b**



R_f (hexane/ethyl acetate 5:1) = 0.38. - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.23-1.34 (m, 4H, $CH_2CH_2CH_3$), 1.37 (quint, *J* = 7.1 Hz, $CH_2CH_2CH_2CH_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.49 (m, 1H, CH_2CHOH), 1.59 (m, 1H, CH_2CHOH), 2.03 (q, *J* = 7.2 Hz, 2H, =$CHCH_2CH_2CH_2CH_2$), 2.15 (m, 2H, CH_2CH_2CHOH), 2.36 (AB part of ABX system, *J* = 16.3, 8.7, 3.5 Hz, 2H, $CH_2COOtBu$), 3.22 (d, *J* = 3.9 Hz, O*H*), 3.96 (m, 1H, C*H*OH), 5.51-5.60 (m, 2H, C*H*=CHCH=C*H*CH_2), 5.95-6.06 (m, 2H, C*H*C*H*=$CHCH_2$). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (q, CH_2CH_3), 22.4 (t, *C*H_2CH_3), 28.0 (q, $C(CH_3)_3$), 28.4 (t, *C*H_2CH_2CHOH), 29.0 (t, *C*$H_2CH_2CH_2CH_3$), 31.3 (t, $CH_3CH_2CH_2$), 32.5 (t, $CH_3(CH_2)_3CH_2$), 36.0 (t, *C*H_2CHOH), 42.2 (t, *C*$H_2COOtBu$), 67.4 (d, *C*HOH), 81.0 (s, *C*$(CH_3)_3$), 130.0 (d, *C*H=$CH(CH_2)_3$), 130.93 (d, CH=*C*$H(CH_2)_2CHOH$ or *C*H=$CH(CH_2)_2CHOH$), 130.94 (d, CH=*C*$H(CH_2)_2CHOH$ or *C*H=$CH(CH_2)_2CHOH$), 132.8 (d, =*C*$H(CH_2)_3$), 172.3 (s, *C*OO). - IR (ATR): $\tilde{\nu}$ = 3462 (w), 3011 (w), 2959 (w), 2926 (m), 2856 (w), 1714 (s), 1455 (w), 1393 (w), 1367 (m), 1301 (w), 1253 (w), 1216 (w), 1150 (s), 1092 (w), 987 (s), 949 (w), 879 (w), 842 (w), 761 (w) cm^{-1}. - MS (EI): *m/z* (%) = 296 (3.8) [M^+], 240 (18) [M^+–$CH_2C(CH_3)_2$], 223 (13) [M^+–$OC(CH_3)_3$], 162 (20), 138 (63) [$H_{11}C_5CH$=CHCH=$CHCH_3$], 105 (38), 79 (47), 67 (46), 57 (100) [$(CH_2)_3CH_3^+$], 43 (18) [*t*Bu^+]. - Combustion analysis: $C_{18}H_{32}O_3$ (296.44): calc. C 72.93, H 10.88; found C 72.76, H 11.09.

***(6E,8Z)-tert*-Butyl 3-hydroxytetradeca-6,8-dienoate *(6E,8Z)*-4-11b**



R_f (hexane/ethyl acetate 5:1) = 0.42. - ^{1}H NMR (400 MHz): δ = 0.89 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.28 (m, 4H, $CH_2CH_2CH_3$), 1.37 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.47 (s, 9H, $(CH_3)_3CO$), 1.51 (m, 1H, CH_2CH_2CHOH), 1.62 (m, 1H, CH_2CH_2CHOH), 2.15 (q, *J* = 7.6 Hz, 2H, =$CHCH_2CH_2CH_2$), 2.24 (m, 2H, CH_2CH_2CHOH), 2.37 (AB part of ABX system, *J* = 16.4, 8.9, 3.2 Hz, 1H, $CH_2COOtBu$), 3.13 (s, 1H, O*H*), 3.97 (m, 1 H, C*H*OH), 5.32 (dt, *J* =

7.5, 10.7 Hz, 1H, =C*H*$CH_2CH_2CH_2$), 5.65 (dt, *J* = 15.1, 7.0 Hz, 1H, =C*H*CH_2CH_2CHOH), 5.93 (t, *J* = 11.0 Hz, 1H, C*H*=$CH(CH_2)_3$), 6.34 (ddd, *J* = 15.1, 11.0, 1.2 Hz, 1H, C*H*=$CHCH_2CH_2CHOH$). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 22.5 (t, CH_2CH_3), 27.7 (t, =$CHCH_2(CH_2)_3$), 28.1 (q, $(CH_3)_3CO$), 28.8 (t, CH_2CH_2CHOH), 29.4 (t, $CHCH_2CH_2CH_2$), 31.5 (t, $CH_2CH_2CH_3$), 36.0 (t, CH_2CH_2CHOH), 42.2 (t, $CH_2COOtBu$), 67.5 (d, *C*HOH), 81.3 (s, $(CH_3)_3CO$), 126.3 (d, *C*H=$CHCH_2CH_2CHOH$), 128.3 (d, *C*H=$CH(CH_2)_3$), 130.7 (d, =*C*H$(CH_2)_3$), 133.3 (d, =*C*HCH_2CH_2CHOH), 172.5 (s, *C*OO). - IR (ATR): $\tilde{\nu}$ = 3448 (w), 3010 (w), 2958 (w), 2926 (m), 2856 (w), 1713 (s), 1456 (w), 1367 (m), 1301 (w), 1253 (w), 1150 (s), 1082 (w), 986 (s), 948 (w), 842 (w), 761 (w) cm^{-1}. - MS (EI): *m/z* (%) = 296 (2) [M^+], 240 (28) [M^+–$CH_2C(CH_3)_2$], 222 (47) [M^+–$HOC(CH_3)_3$], 162 (27), 138 (86) [$H_{11}C_5CH$=$CHCH$=$CHCH_3$], 105 (52), 93 (33), 79 (59), 67 (62), 57 (100) [tBu^+], 41 (71). - Combustion analysis: $C_{18}H_{32}O_3$ (296.44): calc. C 72.93, H 10.88; found C 72.99, H 11.16.

Table 6.1 Significant NMR data of *(6E,8E)*-**4-20a,b** and *(6E,8Z)*-**4-11a,b**.

Product	H3, C3	H6, C6	H9, C9	H8, C8	H7, C7
(6E,8E)-**4-20a**	- 201.7 (s)	5.51 (dt) 129.0 (d)	5.60 (m) 133.4 (d)	6.10 (m) 129.7 (d)	6.10 (m) 131.5 (d)
(6E,8Z)-**4-20a**	- 201.6 (s)	5.60 (dt) 131.3 (d)	5.33 (dt) 131.0 (d)	5.91 (t) 127.9 (d)	6.33 (dd) 126.7 (d)
(6E,8E)-**4-20b**	- 202.4 (s)	5.57 (m) 129.3 (d)	5.57 (m) 133.5 (d)	5.97 (m) 129.8 (d)	5.97 (m) 131.5 (d)
(6E,8Z)-**4-20b**	- 202.3 (s)	5.57 (dt) 131.6 (d)	5.29 (dt) 131.1 (d)	5.87 (t) 128.1 (d)	6.29 (ddd) 126.7 (d)
(6E,8E)-**4-11a**	4.01 (quint) 67.7 (d)	5.51-5.62 (m) 130.7 or 131.0 (d), 132.9 (d)		5.95-6.06 (m) 129.9 (d), 130.7 or 131.0 (d)	
(6E,8Z)-**4-11a**	Not assigned 67.2 (d)	5.67 (m) 133.0 (d)	5.31 (m) 130.5 (d)	5.95 (m) 126.2 (d) 128.2 (d)	6.34 (m)
(6E,8E)-**4-11b**	3.96 (m) 67.4 (d)	5.51-5.60 (m) 130.9 (d), 132.8 (d)		5.95-6.06 (m) 130.0 (d), 130.9 (d)	
(6E,8Z)-**4-11b**	3.97 (m) 67.5 (d)	5.65 (dt) 133.3 (d)	5.32 (dt) 130.7 (d)	5.93 (t) 128.3 (d)	6.34 (ddd) 126.3 (d)

Table 6.2 Dienoate **4-20b** by method A

Entry	Scale mmol	Deprotonation of **4-22** with LDA	Deprotonation of **4-19b**	Equiv. Additive	Formation of **4-24**	**4-20b** (%)
1	1	1.2 equiv./10 min 1.1 equiv. **4-22**	2.2 equiv. LDA/30 min	-[a]	1 h	27
2	1	1.2 equiv./ 30 min 1.1 equiv. **4-22**	2.2 equiv. LDA/30 min	4 HMPA	1.5 h	20
3	2	1.4 equiv./40 min 1.3 equiv. **4-22**	2.2 equiv. LDA/40 min	6 HMPA	3 h	25
4	1	1.2 equiv./25 min 1.1 equiv. **4-22**	1.2 equiv. NaH/30 min 1.1 equiv. BuLi/30 min	-	3 h	0
5	27.2	1.2 equiv./50 min 1.1 equiv. **4-22**	2.2 equiv. LDA/40 min	-[a]	3.5 h	28
6	1.1	1.2 equiv. LiHMDS/1 h 1 equiv. **4-22**	2 equiv. LDA/25 min	-	3.5 h	0

[a] Decalin was used as an internal standard for GC monitoring of substrate consumption.

(6*E*,8*Z*)-*tert*-Butyl 3-oxotetradeca-6,8-dienoate 4-20b via three component coupling (Representative procedure)

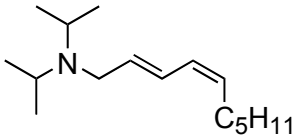
Method A: To a solution of *i*Pr_2NH (0.169 mL, 1.2 mmol) in 5 mL dry THF BuLi (0.75 mL, 1.6*M* in hexanes, 1.2 mmol) was added at –78 °C under a nitrogen atmosphere. After stirring for 20 min at this temperature phosphonium salt **4-22** (524 mg, 1.1 mmol) was added and the resulting brown suspension was warmed to –40 °C during 1 h, with stirring. In another flask BuLi (1.375 mL, 1.6*M* in hexanes, 2.2 mmol) was added to a solution of *i*Pr_2NH (0.311 mL, 2.2 mmol) in 3 mL dry THF at –78 °C and the solution was stirred at this temperature for 30 min. Acetoacetate **4-19b** (174 mg, 1.1 mmol) dissolved in 2 mL dry THF was added via syringe. After stirring for 20 min the mixture was transferred via canula into the flask containing the suspension of butadienylphosphonium salt **4-23**. The resulting mixture was stirred for 1h-3.5 h, while warmed to 0 °C. Hexanal **4-25** (100 mg, 1 mmol) dissolved in 2 mL dry THF was added and the reaction mixture was stirred for additional 30 min. The consumption was monitored by TLC (hexane/EtOAc 5:1). The reaction was quenched with 30 mL ice cold 1% HCl and diluted with diethyl ether. The aqueous layer was extracted 3 times with diethyl ether. The combined ethereal layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated. Purification of the crude mixture (260 mg) by flash chromatography with hexane/ethyl acetate 20:1 gradient to 2:1 afforded the products in following order: A mixture of triphenylphosphine, acetoacetate **4-19b** and ketoester **4-20b**,

followed by pure **4-20b** and finally amine **4-26**. Further purification gave **4-20b** as yellowish oil. Yield: 27% (79 mg), *(6E,8Z)*-**4-20b**:*(6E,8E)*-**4-20b** 3.6:1.

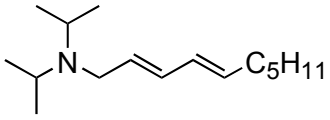
Optimisation experiments under different conditions for the alkylation reaction are presented in Table 6.2.

Method B: The phosphonium salt and the acetoacetate were deprotonated in one pot.

***(2E,4Z)*- and *(2E,4E)*-Deca-2,4-dienyl-*N*,*N*-diisopropylamine *(E,Z)*-4-26 and *(E,E)*-4-26**



***(2E,4Z)*-4-26**



***(2E,4E)*-4-26**

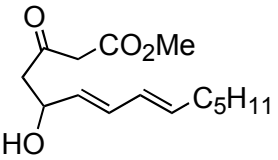
IR: $\tilde{\nu}$ = 3020 (w), 2960 (s), 2926 (s), 2859 (m), 2800 (w), 1722 (w), 1693 (w), 1648 (w), 1609 (w), 1462 (m), 1379 (m), 1363 (m), 1203 (w), 1176 (m), 1138 (w), 1115 (w), 1034 (w), 983 (m), 948 (m), 883 (w), 841 (w), 808 (w), 732 (w). - MS (EI, GC-MS) *m/z* (%): 237 (32) [M^+], 222 (89) [$M^+ - CH_3$], 137 (42), 95 (71), 86 (70), 81 (7), 67 (100). - HRMS: $C_{16}H_{31}N^+$: calc. 237.2456; found 237.2448.

(2E,4Z)-**4-26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 0.93 (d, *J* = 6.6 Hz, 12H, $CH(CH_3)_2$), 1.21-1.35 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.09 (q, *J* = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_2CH_3$), 2.97 (sept, *J* = 6.6 Hz, 2H, $CH(CH_3)_2$), 3.09 (d, *J* = 6.2 Hz, 2H, $CHNCH_2$), 5.26 (dt, *J* = 10.8, 7.6 Hz, 1H, $=CH(CH_2)_3$), 5.59 (dt, *J* = 15.1, 6.3 Hz, 1H, $NCH_2CH=$), 5.91 (t, *J* = 11.0 Hz, 1H, $CH=CH(CH_2)_3$), 6.35 (dd, *J* = 15.1, 11.1 Hz, 1H, $NCH_2CH=CH$). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (q, CH_2CH_3), 20.4 (q, $NCHCH_3$), 22.2 (t, CH_2CH_3), 27.3 (t, $=CHCH_2CH_2$), 29.0 (t, $CH_2CH_2CH_2CH_3$), 31.1 (t, $CH_2CH_2CH_3$), 46.9 (t, $NCH_2CH=$), 47.8 (d, $NCH(CH_3)_2$), 125.5 (d, $NCH_2CH=CH$), 128.1 (d, $(CH_2)_3CH=CH$) 130.3 (d, $=CH(CH_2)_3$), 134.9 (d, $NCH_2CH=$). - *(2E,4E)*-**4-26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 0.96 (d, *J* = 6.6 Hz, 12H, $CH(CH_3)_2$), 1.22-1.37 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.01 (q, *J* = 7.1 Hz, 2H, $CH_2CH_2CH_2CH_2CH_3$), 3.00 (sept, *J* = 6.6 Hz, 2H, $CH(CH_3)_2$), 3.07 (d, *J* = 6.4 Hz, 2H, $CHNCH_2$), 5.56 (m, 2H, $NCH_2CH=CHCH=CH$), 6.02 (m, 2H, $NCH_2CH=CHCH=$). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, CH_2CH_3), 20.6 (q, $NCHCH_3$), 22.5 (t, CH_2CH_3), 29.0 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_3$), 32.5 (t, $=CHCH_2CH_2$), 47.1 (t, $NCH_2CH=$), 48.0 (d, $NCH(CH_3)_2$), 130.1 (d, $NCH_2CH=CH$ or $(CH_2)_3CH=CH$), 130.6 (d, $NCH_2CH=CH$ or $(CH_2)_3CH=CH$), 132.9 (d, $=CH(CH_2)_3$ or $NCH_2CH=$), 133.0 (d, $=CH(CH_2)_3$ or $NCH_2CH=$).

(*6E,8E*)-5-Hydroxy-3-oxo-6,8-tetradecadienoates 4-28a,b (General procedure):

Acetoacetates **4-19a,b** (24 mmol) dissolved in 3 mL dry THF were added dropwise via syringe to a suspension of NaH (1.06 g, 26.4 mmol, 60% in mineral oil) in 50 mL dry THF in a three necked flask at 0 °C under nitrogen. A strong gas evolution was observed, which ceased after 10 min. After 0.5 h of stirring, dry HMPA (5.0 mL, 28.8 mmol) was added to the resulting clear homogeneous reaction at 0 °C. After cooling the reaction mixture to –78 °C, *n*-BuLi (15.8 mL, 25.2 mmol, 1.6*M* in hexanes) was added using a dropping funnel with good stirring over 10 min. The reaction mixture was warmed from –78 °C to –65 °C during 20 min whereupon it turned white inhomogeneous. It was cooled at –78 °C and stirred for another 0.5 h. A solution of **4-27** (3.6 g, 23.6 mmol) dissolved in 7 mL THF was added via syringe over 5 to 10 min with vigorous stirring. The reaction mixture became orange and remained inhomogeneous. The reaction was monitored by TLC with hexane/ethyl acetate 5:1. It was stirred for 0.5 h at –78 °C and then warmed to –45 °C over 1 h during which it became homogenous. The reaction was quenched at –40 °C with 50 mL of a 0.1*M* HCl solution, diluted with 40 mL of diethyl ether and warmed to r.t. The layers were separated, the aqueous was extracted three times with 20 mL diethyl ether. The combined organic layers were washed three times with 30 mL saturated $NaHCO_3$ solution and twice with brine, dried over Na_2SO_4 and concentrated in vacuum to give the crude product. Purification by flash chromatography (hexane/ethyl acetate, gradient 20:1 to 2:1) gave the pure product **4-28a,b** as a mixture of keto and enol tautomers in a ratio of 11:1. The labile product was kept frozen until the next day or used immediately for the next step.

***(6E,8E)*-Methyl 5-hydroxy-3-oxo-6,8-tetradecadienoate 4-28a:**

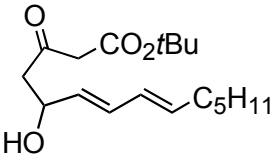


Yield: 5.95 g (94%) as a pale yellow oil, R_f(hexane/ethyl acetate 5:1) = 0.20. - ^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.28 (m, 4H, $CH_2CH_2CH_3$), 1.38 (tt, *J* = 7.7, 7.1 Hz, 2H, CH_2CH_2CH=), 2.06 (q, *J* = 7.2 Hz, 2H, CH_2CH=), 2.77 (m, 2H, CH(OH)CH_2CO), 2.91 (br. s, 1H, O*H*), 3.51 (s, 2H, CH_2COOMe), 3.73 (s, 3H, OCH_3), 4.61 (m, 1H, C*H*OH), 5.55 (dd, *J* = 15.2, 6.3 Hz, 1H, =C*H*CHOH), 5.71 (dt, *J* = 15.2, 6.9 Hz, 1H, CH=C*H*CH_2), 5.99 (dd, *J* = 15.2, 10.4 Hz, 1H, C*H*=$CHCH_2$), 6.22 (dd, *J* = 15.2, 10.5 Hz, 1H, C*H*=CHCHOH). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH_2CH_3), 22.4 (t, CH_2CH_3), 28.7 (t, $CH_2CH_2CH_2CH_3$), 31.2 (t, $CH_2CH_2CH_3$), 32.5 (t, CH_2CH=), 49.60 (t, CH_2COOMe or

CH(OH)*C*H$_2$), 49.61 (t, *C*H$_2$COOMe or CH(OH)*C*H$_2$), 52.3 (q, O*C*H$_3$), 68.1 (d, *C*HOH), 129.0 (d, *C*H=CHCH$_2$), 130.7 (d, =*C*HCHOH), 131.2 (d, *C*H=CHCHOH), 136.2 (d, =*C*HCH$_2$), 167.3 (s, *C*OOCH$_3$), 202.3 (s, CH$_2$*C*OCH$_2$).

Detectable resonances of the enol form: ^{1}H NMR (400 MHz): δ = 2.42 (m, 2H, CH(OH)C*H*$_2$C(OH)=CH), 4.50 (q, *J* = 6.5 Hz, 1H, =CHC*H*OH), 5.07 (s, 1H, =C*H*COOMe). - ^{13}C NMR (100 MHz): δ = 42.9 (t, CH(OH)*C*H$_2$COH), 51.1 (q, O*C*H$_3$), 69.6 (d, *C*HOH), 90.8 (d, =*C*HCOOMe).

***(6E,8E)-tert*-Butyl 5-hydroxy-3-oxo-6,8-tetradecadienoate 4-28b:**



Yield: 5.9 g (81%) as a pale yellow oil, R$_f$(hexane/ethyl acetate 5:1) = 0.25. - ^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 6,9 Hz, 3H, CH$_2$C*H*$_3$), 1.28 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 1.38 (m, 2H, C*H*$_2$CH$_2$CH=), 1.46 (s, 9H, OC(C*H*$_3$)$_3$), 2.06 (q, *J* = 7.2 Hz, 2H, C*H*$_2$CH=CH), 2.75 (m, 2H, CH(OH)C*H*$_2$CO), 3.22 (br. s, 1H, CHO*H*), 3.39 (s, 2H, C*H*$_2$COO*t*Bu), 4.62 (q, *J* = 6.1 Hz, 1H, C*H*OH), 5.56 (dd, *J* = 15.2, 6.4 Hz, 1H, =C*H*CHOH), 5.69 (dt, *J* = 15.1, 7.0 Hz, 1H, CH$_2$C*H*=CH), 6.00 (dd, *J* =15.2, 10.3 Hz, 1H, C*H*=CHCH$_2$), 6.22 (dd, *J* = 15.1, 10.5 Hz, 1H, C*H*=CHCHOH). - ^{13}C NMR (100 MHz): δ = 13.7 (q, *C*H$_3$CH$_2$), 22.2 (t, CH$_3$*C*H$_2$), 27.6 (q, (*C*H$_3$)$_3$CO), 28.6 (t, *C*H$_2$CH$_2$CH), 31.1 (t, CH$_3$CH$_2$*C*H$_2$), 32.3 (t, *C*H$_2$CH=CH), 49.5 (t, CH(OH)*C*H$_2$CO), 51.0 (t, *C*H$_2$COO*t*Bu), 67.9 (d, *C*HOH), 81.7 (s, O*C*(CH$_3$)$_3$), 129.1 (d, CH$_2$CH=*C*H), 130.8 (d, *C*H=CHCHOH), 131.1 (d, =*C*HCHOH), 135.5 (d, CH$_2$*C*H=), 166.0 (s, CH$_2$*C*OO*t*Bu), 202.6 (s, CH$_2$*C*OCH$_2$).

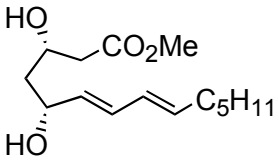
Detectable resonances of the enol form: ^{1}H NMR (400 MHz): δ = 2.38 (m, 2H, CH(OH)C*H*$_2$C(OH)CH), 4.50 (m, 1H, =CHC*H*OH), 4.96 (s, 1H, C=C*H*COO*t*Bu). - ^{13}C NMR (100 MHz): δ = 28.0 (q, (*C*H$_3$)$_3$CO), 42.9 (t, CH(OH)*C*H$_2$COH), 69.2 (d, *C*HOH), 92.3 (d, =*C*HCOOMe).

***syn*-(6E,8E)-3,5-Dihydroxy-6,8-tetradecadienoates 4-30a,b (General procedure):**

To a solution of **4-28a,b** (11.4 mmol) dissolved in 100 mL dry THF/MeOH (4:1), diethyl(methoxy)borane (17.1 mL 1.0*M* solution in THF, 17.1 mmol) was added via syringe at –78 °C over 5 min. The solution was stirred for one hour at –78 to –65 °C. With good stirring, NaBH$_4$ (650 mg, 17.1 mmol) was added in portions at –95 °C. A strong gas evolution was observed that lasted about 0.5 h. The reaction mixture was stirred at –78 °C for 3 h when

it was complete by TLC. The reaction was quenched at with 10 mL of AcOH –78 °C, diluted with 50 mL of diethyl ether, and allowed to warm to r.t. during 15 min. Saturated $NaHCO_3$ solution (100 mL) was added slowly and the mixture was stirred for 5 min. The aqueous layer was extracted three times with 30 mL of diethyl ether. The combined organic layers were washed five times with 30 mL of saturated $NaHCO_3$ solution, twice with 50 mL of brine, dried over Na_2SO_4, concentrated and dried in vacuum to give a crude mixture of the cyclic boronate **4-29a,b** (R_f(hexane/ethyl acetate 2:1) = 0.82) as main product and small amounts of the diols **4-30a,b**. The crude mixture was dissolved in 40 mL of THF/H_2O (3:1) and NaOAc (1.9 g, 23 mmol) was added. The resulting mixture was stirred for 5 min. It was immersed in an ice bath and 12 mL (1.05 mL/mmol) of a 30% solution of H_2O_2 was added slowly with stirring. The mixture was stirred at 0 °C for 0.5 h when it was complete by TLC. At 0 °C, 40 mL of a saturated Na_2SO_3 solution was added slowly, followed by 40 mL of diethyl ether. Stirring was continued at r.t. for 10 min. The layers were separated, the aqueous layer was extracted three times with 25 mL of diethyl ether, the combined organic layers were washed once with water, once with brine, dried over Na_2SO_4 and concentrated to give crude products **4-30a,b**. The almost pure diols were purified by flash chromatography (hexane/ethyl acetate 5:1 and 2:1).

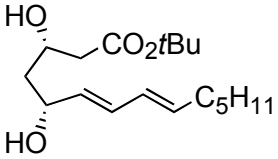
***(3S*,5R*,6E,8E)*-Methyl 3,5-dihydroxy-6,8-tetradecadienoate 4-30a:**



Yield: 2.5 g (81%) as a colourless oil, R_f(hexane/ethyl acetate 2:1) = 0.23. - ^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 6.7 Hz, 3H, C*H*$_3$CH$_2$), 1.20-1.35 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$CH$_2$), 1.39 (m, 2H, C*H*$_2$CH$_2$CH=CH), 1.63 (ddd, *J* = 14.3, 4.0, 3.3 Hz, 1H, CH(OH)C*H*$_2$CH(OH)), 1.73 (ddd, *J* = 14.3, 9.3, 9.2 Hz, 1H, CH(OH)C*H*$_2$CH(OH)), 2.07 (m, 2H, C*H*$_2$CH=CH), 2.50 (AB part of ABX system, *J* = 16.2, 7.4, 4.9 Hz, 2H, C*H*$_2$COOMe), 3.25 (br. s, 1H, O*H*), 3.70 (s, 3H, OC*H*$_3$), 3.84 (br. s, 1H, O*H*), 4.27 (m, 1H, CH$_2$C*H*(OH)CH$_2$), 4.41 (m, 1H, CHC*H*(OH)CH$_2$), 5.55 (dd, *J* = 15.2, 6.7 Hz, 1H, =C*H*CHOH), 5.70 (dt, *J* = 14.4, 6.9 Hz, 1H, CH$_2$C*H*=), 6.00 (m, 1H, CH$_2$CH=C*H*), 6.20 (dd, *J* = 15.2, 10.3 Hz, 1H, C*H*=CHCHOH). - ^{13}C NMR (50 MHz): δ = 14.5 (q, *C*H$_3$CH$_2$), 23.0 (t, CH$_3$*C*H$_2$), 29.4 (t, *C*H$_2$CH$_2$CH), 31.9 (t, CH$_3$CH$_2$*C*H$_2$), 33.1 (t, *C*H$_2$CH=), 42.2 (t, *C*H$_2$COOMe), 43.2 (t, CH(OH)*C*H$_2$CH(OH)), 52.3 (q, O*C*H$_3$), 68.6 (d, CH$_2$*C*H(OH)CH$_2$), 72.7 (d, =CH*C*HOH), 129.8 (d, CH$_2$CH=*C*H), 131.4 (d, *C*H=CHCHOH), 133.0 (d, =*C*HCHOH), 136.3 (d, CH$_2$*C*H=), 173.2 (s, *C*OOMe). - IR (Film):

$\tilde{\nu}$ = 3462 (br. w), 3419 (br. w), 3032 (w), 3003 (w), 2956 (w), 2920 (m), 2853 (w), 1719 (s), 1466 (w), 1435 (m), 1344 (w), 1324 (w), 1306 (w), 1257 (w), 1198 (m), 1172 (m), 1149 (m), 1117 (m), 1064 (m), 1043 (w), 999 (s), 893 (w), 875 (w), 842 (m), 787 (w), 723 (w). - MS(EI) *m/z* (%): 270 (13) [M^+], 252 (18) [M^+–H_2O], 234 (50) [M^+–$2H_2O$], 181 (37) [M^+–C_5H_{11}–H_2O], 179 (20), 163 (10) [M^+–C_5H_{11}–$2H_2O$], 161 (13), 142 (22), 131 (18), 127 (37), 117 (45) [$CH_2CH(OH)CH_2COOMe]^{+\cdot}$, 105 (30) [$(CH{=}CH)_3CH{=}CH_2]^{+\cdot}$, 103 (62) [$CH(OH)CH_2COOMe]^{+\cdot}$, 93 (51), 91 (68), 80 (50), 79 (100), 71 (40) [$C_5H_{11}]^{+\cdot}$, 67 (54), 61 (15), 55 (34), 43 (44) [$C_3H_7]^+$. - Combustion analysis: $C_{15}H_{26}O_4$ (270.36): calc. C 66.64, H 9.69; found C 66.80, H 9.90.

***(3S*,5R*,6E,8E)-tert*-Butyl 3,5-dihydroxy-6,8-tetradecadienoate 4-30b:**

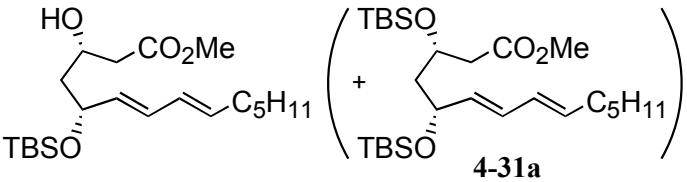


Yield: 2.9 g (81%) as a colourless oil, R_f(hexane/ethyl acetate 2:1) = 0.40. - ^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3H, C*H*$_3$CH$_2$), 1.23-1.33 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$CH$_2$), 1.39 (m, 2H, C*H*$_2$CH$_2$CH=CH), 1.46 (s, 9H, OC(C*H*$_3$)$_3$), 1.60 (ddd, *J* = 14.2, 3.5, 3.1 Hz, 1H, CH(OH)C*H*$_2$CH(OH)), 1.70 (ddd, *J* = 14.2, 9.7, 9.3 Hz, 1H, CH(OH)C*H*$_2$CH(OH)), 2.06 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH=CH), 2.40 (m, 2H, C*H*$_2$COO*t*Bu), 4.21 (m, 1H, CH$_2$C*H*(OH)CH$_2$), 4.42 (m, 1H, CHC*H*(OH)CH$_2$), 5.56 (dd, *J* = 15.2, 6.7 Hz, 1H, =C*H*CHOH), 5.70 (dt, *J* = 15.1, 7.3 Hz, 1H, CH$_2$C*H*=), 6.00 (dd, *J* = 15.1, 10.4 Hz, 1H, CH$_2$CH=C*H*), 6.21 (dd, *J* = 15.2, 10.3 Hz, 1H, C*H*=CHCHOH). - ^{13}C NMR (100 MHz): δ = 14.3 (q, *C*H$_3$CH$_2$), 22.8 (t, CH$_3$*C*H$_2$), 28.4 (q, C(*C*H$_3$)$_3$), 29.2 (t, *C*H$_2$CH$_2$CH), 31.7 (t, CH$_3$CH$_2$*C*H$_2$), 32.9 (t, *C*H$_2$CH=), 42.9 (t, *C*H$_2$COO*t*Bu), 43.1 (t, CH(OH)*C*H$_2$CH(OH)), 68.7 (d, CH$_2$*C*H(OH)CH$_2$), 72.6 (d, =CH*C*HOH), 81.7 (s, O*C*(CH$_3$)$_3$), 129.6 (d, CH$_2$CH=*C*H), 131.1 (d, *C*H=CHCHOH), 132.9 (d, =*C*HCHOH), 136.0 (d, CH$_2$*C*H=), 172.3 (s, *C*OO*t*Bu). - IR (Film): $\tilde{\nu}$ = 3393 (br. w), 2957 (m), 2928 (m), 2858 (w), 1726 (s), 1368 (m), 1301 (w), 1255 (w), 1149 (s), 1067 (m), 988 (s), 844 (m). - MS(EI) *m/z* (%): 312 (0.5) [M^+], 276 (8) [M^+–$2H_2O$], 256 (18) [M^+–$H_2C{=}C(CH_3)_2$], 238 (10) [M^+–H_2O–$H_2C{=}C(CH_3)_2$], 220 (21) [M^+–$2H_2O$–$H_2C{=}C(CH_3)_2$], 179 (12), 167 (18), 151 (14), 131 (14), 128 (17), 113 (26), 105 (18), 91 (36), 79 (55), 67 (25), 57 (100) [*t*Bu]$^+$. - Despite many attempts, neither a satisfactory combustion analysis nor HRMS data could be obtained for this compound.

***(3S*,5R*,6E,8E)*-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxytetradeca-6,8-dienoates 4-12a,b (General procedure):** 2,6-Lutidine (2.9 mL, 24.9 mmol, 3 equiv.) was added to a

solution of **4-30a,b** (8.3 mmol) in 78 mL dry CH_2Cl_2. The mixture was cooled to –78 °C and TBSOTf (2.0 mL, 8.7 mmol) was added dropwise via syringe. The reaction mixture was stirred at –78 °C for 3.5 h and monitored by TLC (hexane/ethyl acetate 2:1, R_f's see below). Substrates **4-30a,b** comigrate with 2,6-lutidine, but differentiation is easy by staining the TLC plate with $KMnO_4$ solution: the diol is stained, but 2,6-lutidine not). The reaction was quenched with 60 mL of saturated $KHSO_4$ solution, diluted with ethyl acetate (100 mL) and allowed to warm to r.t. with stirring. The layers were separated. The aqueous layer was extracted twice with diethyl ether and twice with ethyl acetate. The combined organic layers were washed subsequently with water, saturated $NaHCO_3$ solution and twice with brine. The mixture was dried over Na_2SO_4, evaporated and dried in vacuum to give the crude product, which was purified by flash chromatography (hexane/ethyl acetate 10:1, gradient to 2:1).

***(3S*,5R*,6E,8E)*-Methyl 5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-6,8-tetradecadienoate 4-12a:**

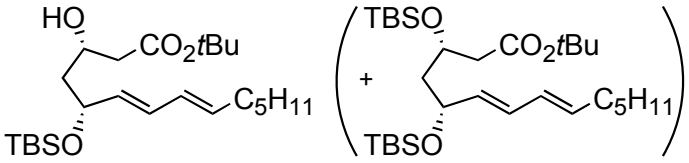


4-31a

The components of the mixture eluted in the following order: Trace amounts of disilyl diether **4-31a,** R_f(hexane/ethyl acetate 2:1) = 0.88; 2.53 g (79%) of **4-12a** as a colourless oil, R_f(hexane/ethyl acetate 2:1) = 0.68; 0.42 g (19%) of substrate **4-30a**, R_f(hexane/ethyl acetate 2:1) = 0.23. - ^{1}H NMR (400 MHz): δ = –0.04 (s, 3H, SiC*H*$_3$), 0.00 (s, 3H, SiC*H*$_3$), 0.80 (t+s, 12H, C*H*$_3$CH$_2$, OSi(C*H*$_3$)$_3$), 1.16-1.26 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$CH$_2$), 1.30 (quint, *J* = 7.1 Hz, 2H, CH$_3$CH$_2$CH$_2$C*H*$_2$), 1.53 (ddd, *J* = 14.0, 5.2, 3.0 Hz, 1H, C*H*$_2$CHOTBS), 1.67 (ddd, *J* = 14.0, 9.1, 8.0 Hz, 1H, C*H*$_2$CHOTBS), 1.98 (dq, *J* = 0.9, 7.8 Hz, 2H, C*H*$_2$CH=), 2.39 (AB part of ABX, *J* = 15.8, 7.5, 5.2 Hz, 2H, C*H*$_2$COOMe), 3.47 (d, *J* = 2.3 Hz, 1H, CHO*H*), 3.60 (s, 3H, OC*H*$_3$), 4.09 (m, 1H, C*H*OH), 4.31 (dt, *J* = 7.3, 5.4 Hz, 1H, C*H*OTBS), 5.40 (dd, *J* = 15.1, 7.4 Hz, 1H, =C*H*CHOTBS), 5.59 (dt, *J* = 14.3, 6.9 Hz, 1H, CH$_2$C*H*=), 5.89 (ddt, *J* = 10.4, 14.9, 1.3 Hz, 1H, CH$_2$CH=C*H*), 6.01 (dd, *J* = 10.3, 15.1 Hz, 1H, C*H*=CHCHOTBS). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si*C*H$_3$), –3.9 (q, Si*C*H$_3$), 14.0 (q, *C*H$_3$CH$_2$), 18.0 (s, Si*C*(CH$_3$)$_3$), 22.5 (t, CH$_3$*C*H$_2$), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.8 (t, *C*H$_2$CH$_2$CH), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 32.6 (t, CH$_2$*C*H$_2$CH), 41.7 (t, *C*H$_2$COOMe), 44.3 (t, *C*H$_2$CHOTBS), 51.6 (q, O*C*H$_3$), 66.9 (d, *C*HOH), 73.4 (d, *C*HOTBS), 129.2 (d, CH$_2$CH=*C*H), 130.8 (d, *C*H=CHCHOTBS), 133.0 (d, =*C*HCHOTBS), 135.7 (d, CH$_2$*C*H=), 172.6 (s, *C*OOMe). - IR (Film): $\tilde{\nu}$ = 3520 (br. w), 3019 (w), 2955 (s), 2929 (s), 2857 (m), 1739 (s), 1467 (w), 1439 (w), 1363 (w), 1254 (m), 1199

(w), 1169 (w), 1073 (m), 990 (s), 880 (w), 836 (s), 777 (s). - MS(EI) *m/z* (%): 384 (1) [M^+], 327 (5), 295 (5), 267 (9), 253 (8), 235 (12), 203 (7), 175 (10), 161 (12), 135 (19), 133 (9), 105 (10), 91 (18), 79 (21), 75 (100). - HRMS: $C_{21}H_{40}O_4Si$: calc. 384.2696; found 384.2687. - Combustion analysis: $C_{21}H_{40}O_4Si$ (384.63): calc. C 65.58, H 10.48; found C 65.56, H 10.84.

***(3S*,5R*,6E,8E)-tert*-Butyl 5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-6,8-tetradecadienoate 4-12b:**



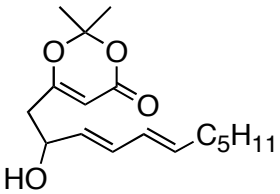
4-31b

In this case, 1.2 equiv. of TBSOTf was used. The components of the mixture eluted in the following order: 0.99 g (22%) of disilyl diether **4-31b** as a colourless oil, R_f (hexane/ethyl acetate 5:1) = 0.8; 2.3 g (65%) of **4-12b** as a colourless oil, R_f (hexane/ethyl acetate 5:1) = 0.55. - ^{1}H NMR (400 MHz): δ = –0.04 (s, 3H, SiC*H*$_3$), 0.00 (s, 3H, SiC*H*$_3$), 0.81 (t+s, 12H, C*H*$_3$CH$_2$, OSiC(C*H*$_3$)$_3$), 1.10-1.25 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$CH$_2$), 1.35 (m, 2H, CH$_3$CH$_2$CH$_2$C*H*$_2$), 1.37 (s, 9H, OC(C*H*$_3$)$_3$), 1.51 (ddd, *J* = 13.9, 5.8, 3.4 Hz, 1H, C*H*$_2$CHOTBS), 1.67 (ddd, *J* = 13.9, 9.0, 7.5 Hz, 1H, C*H*$_2$CHOTBS), 1.99 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH=), 2.30 (AB part of ABX, *J* = 16.0, 7.0, 5.5 Hz, 2H, C*H*$_2$COO*t*Bu), 3.40 (d, *J* = 2.7 Hz, 1H, CHO*H*), 4.01 (m, 1H, C*H*OH), 4.30 (q, *J* = 6.8 Hz, 1H, C*H*OTBS), 5.41 (dd, *J* = 15.1, 7.3 Hz, 1H, =C*H*CHOTBS), 5.59 (dt, *J* = 14.4, 6.9 Hz, 1H, CH$_2$C*H*=), 5.90 (dd, *J* = 14.9, 10.4 Hz, 1H, CH$_2$CH=C*H*), 6.02 (dd, *J* = 15.0, 10.4 Hz, 1H, C*H*=CHCHOTBS). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si*C*H$_3$), –4.0 (q, Si*C*H$_3$), 14.0 (q, *C*H$_3$CH$_2$), 18.0 (s, Si*C*(CH$_3$)$_3$), 22.5 (t, CH$_3$*C*H$_2$CH$_2$), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 28.8 (t, *C*H$_2$CH$_2$CH), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 32.6 (t, *C*H$_2$CH=), 42.7 (t, *C*H$_2$COO*t*Bu), 44.5 (t, *C*H$_2$CHOTBS), 66.6 (d, *C*HOH), 72.8 (d, *C*HOTBS), 80.8 (s, O*C*(CH$_3$)$_3$), 129.3 (d, CH$_2$CH=*C*H), 130.7 (d, *C*H=CHCHOTBS), 133.2 (d, =*C*HCHOTBS), 135.6 (d, CH$_2$*C*H=), 171.7 (s, *C*OO*t*Bu). - IR (Film): $\tilde{\nu}$ = 3516 (br. w), 2956 (w), 2929 (s), 2857 (w), 1728 (m), 1467 (w), 1367 (w), 1253 (m), 1151 (s), 1070 (m), 988 (s), 834 (s), 775 (s), 669 (w). - MS(ESI) *m/z* (%): 876 (5) [2M+Na^+–H^+], 875 (8) [2M+Na^+–2H], 450 (26) [M+Na^+], 449 (100) [M+Na^+–H]. - Combustion analysis: $C_{24}H_{46}O_4Si$ (426.71): calc. C 67.55, H 10.87; found C 67.77, H 11.12.

***(3S*,5R*,6E,8E)-tert*-Butyl 3,5-(di-*tert*-butyldimethylsilyloxy)-6,8-tetradecadienoate 4-31b:**

^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, SiCH_3), 0.036 (s, 3H, SiCH_3), 0.043 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3), 0.86 (t+s, 12H, CH_3CH$_2$, OSiC(CH_3)$_3$), 0.87 (s, 9H, OSiC(CH_3)$_3$), 1.23-1.32 (m, 4H, CH$_3$CH_2CH_2CH$_2$), 1.36 (m, 2H, CH$_3$CH$_2$CH$_2$CH_2), 1.41 (s, 9H, OC(CH_3)$_3$), 1.61 (m, 1H, CH_2CH(OTBS)CH=), 1.77 (m, 1H, CH_2CH(OTBS)CH=), 2.05 (q, *J* = 6.9 Hz, 2H, CH_2CH=), 2.37 (AB part of ABX, *J* = 14.8, 6.5, 5.4 Hz, 2H, CH_2COO*t*Bu), 4.14 (dt, *J* = 11.9, 6.2 Hz, 1H, C*H*(OTBS)CH$_2$COO*t*Bu), 4.19 (q, *J* = 6.6 Hz, 1H, =CHC*H*OTBS), 5.47 (dd, *J* = 14.9, 6.9 Hz, 1H, =C*H*CHOTBS), 5.62 (dt, *J* = 14.7, 6.1 Hz, 1H, CH$_2$C*H*=), 5.96 (dd, *J* = 14.9, 10.4 Hz, 1H, CH$_2$CH=C*H*), 6.02 (dd, *J* = 14.9, 10.6 Hz, 1H, C*H*=CHCHOTBS). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si*C*H$_3$), –4.5 (q, Si*C*H$_3$), –4.1 (q, Si*C*H$_3$), 14.0 (q, *C*H$_3$CH$_2$), 17.9 (s, Si*C*(CH$_3$)$_3$), 18.1 (s, Si*C*(CH$_3$)$_3$), 22.5 (t, CH$_3$*C*H$_2$CH$_2$), 25.86 (q, SiC(*C*H$_3$)$_3$), 25.91 (q, SiC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 28.9 (t, *C*H$_2$CH$_2$CH), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 32.6 (t, *C*H$_2$CH=), 43.8 (t, *C*H$_2$COO*t*Bu), 46.1 (t, *C*H$_2$CH(OTBS)CH=), 66.7 (d, *C*H(OTBS)CH$_2$COO*t*Bu), 72.6 (d, =CH*C*HOTBS), 80.0 (s, O*C*(CH$_3$)$_3$), 129.6 (d, CH$_2$CH=*C*H), 130.2 (d, *C*H=CHCHOTBS), 133.7 (d, =*C*HCHOTBS), 134.7 (d, CH$_2$*C*H=), 170.6 (s, *C*OO*t*Bu). - IR (ATR): $\tilde{\nu}$ = 2956 (w), 2929 (m), 2857 (w), 1733 (m), 1468 (w), 1366 (w), 1253 (m), 1153 (m), 1084 (m), 987 (m), 955 (w), 894 (w), 833 (s), 809 (m), 774 (s). - MS(ESI) *m/z* (%): 563 (100) [M+Na$^+$], 449 (100) [M–TBS+Na$^+$+H]. - Combustion analysis: $C_{30}H_{60}O_4Si_2$ (540.97): calc. C 66.61, H 11.18; found C 66.93, H 11.37.

_(E,E)_-6-(2-Hydroxyundeca-3,5-dienyl)-2,2-dimethyl-4_H_-1,3-dioxin-4-one 4-33 via vinylogous aldol addition under basic conditions (General procedure):



To a solution of 0.42 mL (3 mmol) *i*Pr$_2$NH in 8 mL dry THF, 1.87 mL (3 mmol) *n*-BuLi (1.6*M* in *n*-hexane) was added at −78 °C under a nitrogen atmosphere. After stirring for 20 min a solution of 0.40 mL (3 mmol) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **4-32** in 1 mL dry THF was added. After stirring for 30 min at −78 °C, 0.35 mL (2 mmol) of (2*E*,4*E*)-deca-2,4-dienal **4-27** dissolved in 1 mL dry THF was added at the given temperature (Table 4.4). The reaction was stirred until complete by TLC. The reaction mixture was quenched with a few drops of saturated NH$_4$Cl solution, warmed to r.t., and diluted with diethyl ether. The layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined etheral layers were washed with water, dried over Na$_2$SO$_4$ and concentrated in vacuum. The

product was purified by flash chromatography (hexane/ethyl acetate 5:1, gradient to 1:1). The Michael adduct **4-34** eluted first, followed by product **4-33**. For yields see Table 4.4.

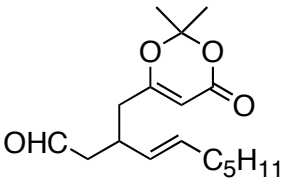
(*E,E*)-6-(2-Hydroxyundeca-3,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one 4-33 via vinylogous Mukaiyama aldol addition:

2,2-Dimethyl-6-methylene-4-(trimethylsilyloxy)-1,3-dioxine **4-35** (1.8 g, 8.5 mmol) in 20 mL dry CH_2Cl_2 was added dropwise to a solution of 1.05 mL (5.1 mmol) (2*E*,4*E*)-2,4-decadienal **4-27** (85% purity) and 0.59 mL (5.4 mmol) $TiCl_4$ in 40 mL dry CH_2Cl_2 at −78 °C. The homogenous red solution changed to a dark colour. The consumption was monitored by TLC (hexane/ethyl acetate 3.5:1 (R_f(**4-27**) = 0.59, R_f(**4-32**) = 0.22)). After 35 min another 0.17 mL (0.8 mmol) of **4-27** was added and stirring was continued at −78 °C for 1.5 h. The reaction mixture was quenched with 20 mL of a sat'd $NaHCO_3$ solution and warmed to r.t. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude oily product was purified by flash chromatography (hexane/ethyl acetate 5:1, gradient to 2:1). Some **4-32** eluted first with hexane/ethyl acetate 5:1 followed by 1.64 g (94% based on **4-27**) of **4-33** as a pale yellow oil that crystallises slowly.

R_f(hexane/ethyl acetate 2:1) = 0.34. - m.p. 47-49 °C. - ^{1}H NMR (400 MHz): δ = 0.85 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.19-1.30 (m, 4H, $CH_2CH_2CH_3$), 1.35 (quint, *J* = 7.2 Hz, 2H, CH_2CH_2CH), 1.64 (s, 3H, $OCCH_3$), 1.65 (s, 3H, $OCCH_3$), 2.04 (q, *J* = 7.1 Hz, 2H, CH_2CH=), 2.29 (br. s, 1H, OH), 2.42 (AB part of ABX system, *J* = 14.4, 7.6, 5.5 Hz, 2H, $CH(OH)CH_2CO$), 4.39 (dt, *J* = 6.8, 6.4 Hz, 1H, CHOH), 5.28 (s, 1H, $C(O)=CHCO_2$), 5.52 (dd, *J* = 15.2, 6.8 Hz, 1H, =CHCHOH), 5.70 (dt, *J* = 15.1, 6.9 Hz, 1H, CH_2CH=), 5.96 (dd, *J* = 15.1, 10.4 Hz, 1H, CH_2CH=CH), 6.19 (dd, *J* = 15.2, 10.4 Hz, 1H, CH=CHCHOH). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 22.4 (t, CH_2CH_3), 24.9 (q, $OCCH_3$), 25.3 (q, $OCCH_3$), 28.7 (t, $CH_2CH_2CH_2CH_3$), 31.3 (t, $CH_2CH_2CH_3$), 32.5 (t, CH_2CH=), 41.5 (t, $CH(OH)CH_2CO$), 69.6 (d, CHOH), 95.2 (d, $C(O)=CHCO_2$), 106.7 (s, $C(CH_3)_2$), 128.8 (d, $CH_2CH=CH$), 130.9 (d, =CHCHOH), 132.3 (d, CH=CHCHOH), 137.0 (d, CH_2CH=), 161.2 (s, $=CHCO_2$), 168.5 (s, $CH_2C(O)=CH$). - IR (Film): $\tilde{\nu}$ = 3443 (w), 3023 (w), 2997 (w), 2959 (m), 2922 (m), 2853 (m), 1693 (s), 1629 (s), 1392 (s), 1379 (s), 1336 (w), 1279 (s), 1254 (m), 1201 (s), 1097 (w), 1044 (m), 1016 (s), 990 (s), 906 (m), 876 (w), 840 (w), 811 (s), 618 (m) cm^{-1}. - MS (EI): *m/z* (%) = 294 (2) [M^+], 276 (<1) [M^+–H_2O], 236 (52) [M^+–$OC(CH_3)_2$], 218 (12) [M^+–H_2O–$OC(CH_3)_2$], 208 (9) [M^+–$C(CH_3)_2OC$=O], 192 (20) [M^+–$OC(CH_3)_2OC$=O], 190 (14), 179 (9) [M^+–$OC(CH_3)_2OC(=O)CH$], 165 (16), 153 (29) [M^+–

$C_5H_{11}CH=CHCH=CHCHOH]$, 150 (12), 137 (17), 126 (39), 121 (11), 111 (16), 98 (25), 95 (30), 84 (100), 79 (37), 69 (28), 67 (46), 59 (16) $[HOC(CH_3)_2^+]$, 55 (23), 44 (8). - HRMS: $C_{17}H_{26}O_4$: calc. 294.1831; found 294.1822. - Combustion analysis: $C_{17}H_{26}O_4$ (294.39): calc. C 69.36, H 8.90; found C 69.68, H 9.10.

(*E and Z*)-6-(2-(2-oxoethyl)-3-nonenyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one 4-34:

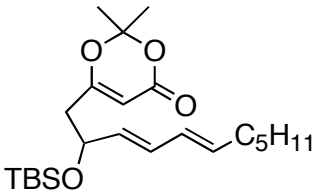


R_f(hexane/ethyl acetate 2:1) = 0.46. - IR (Film): $\tilde{\nu}$ = 3100 (w), 2997 (w), 2957 (m), 2926 (s), 2856 (m), 2722 (w), 1721 (s), 1632 (s), 1389 (s), 1375 (s), 1270 (s), 1251 (m), 1202 (s), 1012 (s), 971 (w), 901 (m), 837 (w), 803 (m) cm^{-1}. - MS (EI): *m/z* (%) = 294 (<1) $[M^+]$, 236 (30) $[M^+–OC(CH_3)_2]$, 218 (9) $[M^+–H_2O–OC(CH_3)_2]$, 207 (35) $[M^+–OC(CH_3)_2–Et]$, 193 (25) $[M+H^+–OC(CH_3)_2OC=O]$, 175 (8) $[M^+–OC(CH_3)_2OC=O–OH]$, 161 (16), 152 (21) [M^+–2,2,6-Trimethyl-1,3-dioxin-4-one–H], 137 (49), 124 (61), 112 (30), 98 (59), 95 (34), 91 (27), 84 (92), 79 (50), 69 (100), 67 (61), 55 (55), 44 (21), 43 (89). - MS (ESI): *m/z* (%) = 317 $[M+Na^+]$. - HRMS: $C_{17}H_{26}O_4Na^+$: calc. 317.1723; found 317.1722.

(E)-Isomer: ^{1}H NMR (400 MHz): δ = 0.80 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.13-1.28 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.59 (s, 3H, $OCCH_3$), 1.61 (s, 3H, $OCCH_3$), 1.90 (m, 2H, $CH_2CH=$), 2.17 (A part of ABX system, *J* = 14.3, 8.8 Hz, 1H, $CH_2C(O)=CH$), 2.29 (B part of ABX system, *J* = 14.2, 5.6 Hz, 1H, $CH_2C(O)=CH$), 2.42 (dd, *J* = 6.9, 1.9 Hz, 2H, CH_2CHO), 2.89 (m, 1H, $CHCH_2CHO$), 5.15 (s, 1H, CHCOO), 5.18 (ddt, *J* = 15.3, 8.3, 1.4 Hz, 1H, $CH_2CH=CH$), 5.45 (ddt, *J* = 14.7, 6.8, 1.1 Hz, 1H, $CH_2CH=$), 9.64 (t, *J* = 1.9 Hz, 1H, CHO). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH_2CH_3), 22.3 (t, CH_2CH_3), 24.9 (q, $OCCH_3$), 25.3 (q, $OCCH_3$), 28.8 (t, $CH_2CH_2CH=$), 31.2 (t, $CH_2CH_2CH_3$), 32.2 (t, $CH_2CH=$), 34.4 (d, $CHCH_2CHO$), 39.0 (t, $CH_2C(O)=$), 48.3 (t, CH_2CHO), 94.7 (d, $C(O)=CHCOO$), 106.5 (s, $C(CH_3)_2$), 129.9 (d, $CH=CHCH$), 133.2 (d, $CH=CHCH$), 160.8 (s, COO), 169.2 (s, $CH_2C(O)=CH$), 200.8 (d, CHO).

Detectable resonances of *(Z)*-Isomer: ^{1}H NMR (400 MHz): δ = 5.18 (m, 1H, =CH), 5.45 (m, 1H, $CH=$). - ^{13}C NMR (100 MHz): δ = 24.86 (q, $OCCH_3$), 25.2 (q, $OCCH_3$), 27.6 (t, $CH_2CH_2CH=$), 29.1 (t, $CH_2CH=$), 31.5 (t, $CH_2CH_2CH_3$), 39.2 (t, $CH_2C(O)=$), 48.7 (t, CH_2CHO), 94.7 (d, $C(O)=CHCOO$), 106.3 (s, $C(CH_3)_2$), 129.6 (d, $CH=CHCH$), 132.6 (d, $CH=CHCH$), 161.7 (s, COO), 200.6 (d, CHO).

***(E,E)*-6-[(2-*tert*-Butyldimethylsilyloxy)undeca-3,5-dienyl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one 4-36:**



To a yellow solution of 1.0 g (3.40 mmol) dioxinone **4-33**, 580 mg (8.50 mmol, 2.5 equiv.) imidazole and 41 mg (0.34 mmol) DMAP in 10 mL dry CH_2Cl_2 was added 615 mg (4.10 mmol, 1.2 equiv.) TBSCl at r.t. A precipitate formed immediately. The mixture was stirred at r.t. for 4.5 h when it was complete by TLC (hexane/ethyl acetate 20:1 and 5:1). The reaction mixture was quenched with 2 mL water, extracted with diethyl ether and the combined ethereal layers were washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to give 1.60 g of a pale yellow oil, which was purified by flash chromatography (hexane/ethyl acetate 20:1, gradient to 5:1). Yield 1.10 g (80%) as a colourless oil.

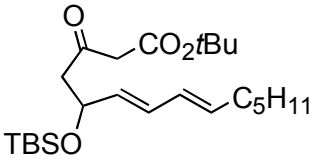
Table 6.3 Optimisation of silylation conditions of crude aldol product **4-33**

Entry	Scale (mmol)	Reaction time (min)	**4-36** (%)	**4-37** (%)
1	1.3	150	62	13
2	1.1	90	72	10
3	7.0	60	65	7

R_f(hexane/ethyl acetate 10:1) = 0.68. - ^{1}H NMR (400 MHz): δ = –0.07 (s, 3H, Si(C*H*$_3$)$_2$), –0.05 (s, 3H, Si(C*H*$_3$)$_2$), 0.78 (s, 9H, SiC(C*H*$_3$)$_3$), 0.82 (m, 3H, CH_2CH_3), 1.16-1.25 (m, 4H, $CH_2CH_2CH_3$), 1.29 (tt, *J* = 14.3, 7.2 Hz, 2H, CH_2CH_2CH), 1.56 (s, 3H, OCC*H*$_3$), 1.58 (s, 3H, OCC*H*$_3$), 1.97 (dt, *J* = 7.2, 7.3 Hz, 2H, CH_2CH=), 2.30 (AB part of ABM system, *J* = 14.0, 7.0, 5.4 Hz, 2H, TBSOCHC*H*$_2$CO), 4.31 (dt, *J* = 6.6, 6.2 Hz, 1H, C*H*OTBS), 5.16 (s, 1H, C(O)=C*H*CO$_2$), 5.39 (dd, *J* = 15.1, 6.9 Hz, 1H, =C*H*CHOTBS), 5.59 (dt, *J* = 14.6, 7.2 Hz, 1H, CH_2CH=), 5.88 (dd, *J* = 15.0, 10.5 Hz, 1H, CH_2CH=C*H*), 6.02 (dd, *J* = 15.0, 10.5 Hz, 1H, C*H*=CHCHOTBS). - ^{13}C NMR (50 MHz): δ = –4.3 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH_2CH_3), 18.0 (s, Si*C*(CH$_3$)$_3$), 22.4 (t, *C*H$_2$CH$_3$), 24.6 (q, OC*C*H$_3$), 25.6 (q, OC*C*H$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.4 (t, *C*H$_2$CH$_2$CH$_3$), 32.6 (t, *C*H$_2$CH=), 43.1 (t, TBSOCH*C*H$_2$CO), 70.5 (d, *C*HOTBS), 95.3 (d, C(O)=*C*HCO$_2$), 106.3 (s, *C*(CH$_3$)$_2$), 128.9 (d, CH_2CH=*C*H), 131.1 (d, =*C*HCHOTBS), 131.9 (d, *C*H=CHCHOTBS), 136.0 (d, CH_2*C*H=), 161.1 (s, =CH*C*O$_2$), 168.5 (s, CH$_2$*C*(O)=CH). - IR (Film): $\tilde{\nu}$ = 3000 (w), 2957 (m), 2928 (w), 2856 (w), 1732 (s), 1636 (m), 1465 (w), 1375 (m), 1272 (m), 1251 (m), 1203 (m), 1067 (m), 1011

(m), 989 (s), 899 (w), 832 (s), 807 (s), 774 (s) cm^{-1}. - MS (EI): *m/z* (%) = 408 (<1) [M^+], 350 (4) [M^+–$OC(CH_3)_2$], 293 (87) [M^+–TBS], 267 (53) [M^+–6-methylene-2,2-dimethyl-1,3-dioxin-4-one], 251 (8), 225 (4), 195 (5), 169 (7), 147 (7), 143 (12), 141 (45) [6-methylene-2,2-dimethyl-1,3-dioxin-4-one$^+$], 115 (7) [TBS^+], 99 (33), 79 (20), 73 (100), 69 (15), 59 (10), 43 (37). - Combustion analysis: $C_{23}H_{40}O_4Si$ (408.65): calc. C 67.60, H 9.87; found C 67.69, H 10.03.

***(6E,8E)-tert*-Butyl 5-(*tert*-butyldimethylsilyloxy)-3-oxotetradeca-6,8-dienoate 4-38:**



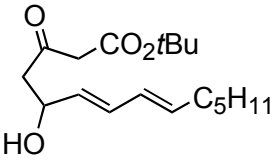
The TBS-protected dioxinone **4-36** (1.0 g, 2.45 mmol) was refluxed in 25 mL dry *tert*-butanol under an argon atmosphere at 150 °C bath temperature for 32 hours when finished by TLC (hexanes/ethyl acetate 10:1). The colourless solution was evaporated. The remaining oil was purified by flash chromatography (hexanes/ethyl acetate 10:1). Yield 1.0 g (96%) **4-33** and 50 mg of recovered dioxinone **4-36**.

R_f(hexanes/EtOAc 10:1) = 0.52. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.84 (s, 9H, SiC(C*H*$_3$)$_3$), 0.86 (t, *J* = 6.6 Hz, 3H, CH_2CH_3), 1.23-1.29 (m, 4H, $CH_2CH_2CH_3$), 1.36 (quint, *J* = 7.1 Hz, 2H, CH_2CH_2CH=), 1.43 (s, 9H, OC(C*H*$_3$)$_3$), 2.03 (q, *J* = 7.1 Hz, 2H, CH_2CH=), 2.55 (A part of ABX system, *J* = 15.1, 4.9 Hz, 1H, TBSOCHC*H*$_2$CO), 2.75 (B part of ABX system, *J* = 15.1, 7.7 Hz, 1H, TBSOCHC*H*$_2$CO), 3.34 (s, 2H, $CH_2COOtBu$), 4.60 (dt, *J* = 5.0, 6.9 Hz, 1H, CHOTBS), 5.48 (dd, *J* = 15.2, 6.7 Hz, 1H, TBSOCHC*H*=), 5.65 (dt, *J* = 15.1, 6.9 Hz, 1H, CH_2CH=), 5.94 (dd, *J* = 15.1, 10.4 Hz, 1H, CH_2CH=C*H*), 6.11 (dd, *J* = 15.2, 10.4 Hz, 1H, TBSOCHCH=C*H*). - ^{13}C NMR (100 MHz): δ = –5.0 (q, Si(C*H*$_3$)$_2$), –4.4 (q, Si(C*H*$_3$)$_2$), 14.0 (q, CH_2CH_3), 18.1 (s, SiC(CH$_3$)$_3$), 22.5 (t, CH_2CH_3), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.0 (q, OC(*C*H$_3$)$_3$), 28.8 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_3$), 32.6 (t, CH_2CH=), 51.2 (t, TBSOCH*C*H$_2$CO), 52.1 (t, $CH_2COOtBu$), 70.1 (d, *C*HOTBS), 81.7 (s, O*C*(CH$_3$)$_3$), 129.2 (d, CH_2CH=*C*H), 130.5 (d, *C*H=CHCHOTBS), 132.4 (d, =*C*HCHOTBS), 135.6 (d, CH_2CH=), 166.2 (s, COO), 201.5 (s, $CHCH_2C$=O). - IR (Film): $\tilde{\nu}$ = 2956 (m), 2928 (s), 2857 (m), 1745 (w), 1717 (m), 1648 (w), 1476 (w), 1409 (w), 1367 (w), 1318 (w), 1250 (m), 1144 (m), 1070 (m), 988 (m), 942 (w), 832 (s), 807 (m), 776 (s) cm^{-1}. - MS (EI): *m/z* (%) = 424 (<1) [M^+], 368 (6) [M^+–CH_2=$C(CH_3)_2$], 311 (17), 293 (12) [M^+–OTBS], 267 (30) [M^+–$CH_2COCH_2CO_2tBu$], 215 (8), 187 (7) [$HOCHCH_2COCH_2CO_2tBu^+$], 177 (8) [M^+–TBSO–CH_3CO_2tBu], 159 (100)

[$CH_3COCH_2CO_2tBu+H^+$], 153 (27) [$C_5H_{11}(CH=CH)_2CHOH^+$], 143 (12) [$COCH_2CO_2tBu^+$], 135 (8), 115 (13) [TBS^+], 91 (9), 75 (82), 73 (30), 57 (25), 43 (7), 41 (22). - HRMS: $C_{24}H_{44}O_4Si$: calc. 424.3009; found 424.2988. - Combustion analysis: $C_{24}H_{44}O_4Si$ (424.69): calc. C 67.87, H 10.44; found C 67.66, H 10.48.

Detectable resonances of the enol form: ^1H NMR (400 MHz): δ = –0.02 (s, 3H, Si(C*H*$_3$)$_2$), –0.01 (s, 3H, Si(C*H*$_3$)$_2$), 1.44 (s, 9H, OC(CH$_3$)$_3$), 2.25 (m, 2H, TBSOCHC*H*$_2$COH), 4.46 (m, 1H, C*H*OTBS), 4.88 (s, 1H, =CHCOO*t*Bu), 5.48 (m, 1H, TBSOCHC*H*=), 5.65 (m, 1H, CH$_2$C*H*=), 5.94 (m, 1H, CH$_2$CH=C*H*), 6.11 (m, 1H, TBSOCHCH=C*H*). - ^{13}C NMR (100 MHz): δ = –5.3 (q, Si(CH$_3$)$_2$), –4.5 (q, Si(CH$_3$)$_2$), 18.2 (s, Si*C*(CH$_3$)$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.3 (q, OC(*C*H$_3$)$_3$), 44.7 (t, TBSOCH*C*H$_2$COH), 70.3 (d, *C*HOTBS), 80.5 (s, O*C*(CH$_3$)$_3$), 93.0 (d, *C*HCOO*t*Bu), 129.4 (d, CH$_2$CH=*C*H), 130.1 (d, *C*H=CHCHOTBS), 133.0 (d, =*C*HCHOTBS), 135.1 (d, CH$_2$*C*H=), 172.5 (s, CO$_2$*t*Bu), 174.2 (s, CH$_2$*C*OH).

***(6E,8E)-tert*-Butyl 5-hydroxy-3-oxo-6,8-tetradecadienoate 4-28b from 4-38:**



To a solution of 600 mg (1.41 mmol) **4-38** in 10 mL dry THF was added consecutively 0.086 mL (1.5 mmol) glacial AcOH and 3 mL (3.00 mmol) of a 1*M* TBAF solution in THF at 0 °C. The mixture was warmed to r.t. and stirred for 4 h when finished by TLC (hexanes/ethyl acetate 2:1). The reaction mixture was diluted with diethyl ether, 0.25 mL of water was added and the mixture was filtered through a pad of silica gel. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate 5:1, gradient to 2:1) to give 385 mg (88%) of **4-28b** as colourless oil.

6.9.2. Oxidative cyclisation of 3-hydroxy esters 4-11a,b and 4-12a,b

Oxidative cyclisations of 3-hydroxyester dianions 4-11a,b (General procedures):

Procedure A: Anhydrous LiCl (234 mg, 5.53 mmol or 402 mg, 9.5 mmol) was heated in vacuum with stirring 3-5 times for 3 min at 10 min intervals. It was dissolved in 18 mL dry THF under nitrogen (only in two experiments, Table 4.9, entries 4 and 6). All the other experiments began directly with the preparation of LDA. To 18 mL dry THF 0.230 mL (1.62 mmol, 2.5 equiv.) *i*Pr$_2$NH and 1.01 mL (1.62 mmol, 2.5 equiv.) BuLi (1.6*M* in hexane) were added subsequently at –78 °C. The resulting mixture was stirred for 30 min. Esters **4-11a,b**

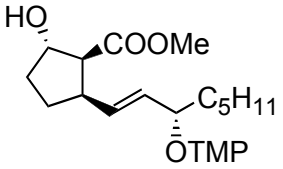
(0.79 mmol) dissolved in 1 mL dry THF were added dropwise to the LDA solution at –78 °C. The vial was rinsed with 1 mL THF. The mixture was warmed from –78 to –30 °C during 1 h, and stirred at –30 °C for 20 min. After cooling to –78 °C, 0.868 mL (4.99 mmol) HMPA was added dropwise followed by addition of 148 mg (0.95 mmol) TEMPO **1-2** as a solid. Sometimes HMPA precipitated, therefore the acetone bath was taken away shortly (2 min) until the HMPA dissolved. The mixture was stirred at –78 °C for 5 min and $FeCp_2PF_6$ **1-3** was added in small portions with vigorous stirring. Each portion was added after consumption of the previous as monitored by the disappearence of the blue colour (About 392 mg of **1-3** were added in 10 min, when the reaction mixture remained blue and inhomogeneous. Two additional spatula tips of **1-3** were added subsequently). After the addition was complete, the reaction mixture was stirred at –78 - –70 °C for 20 min.

Procedure B: A 20% solution of *t*BuMgCl in THF (0.754 mL, 1.2 mmol) was added via syringe to a solution of esters **4-11a,b** (1 mmol) in 5 mL dry THF at –78 °C. The mixture was stirred for 30 min at –78 - –50 °C. After cooling to –78 °C, 0.65 mL of a 2*M* LDA solution in THF/*n*-heptane (1.3 mmol) was added and the mixture was stirred at –78 to –40 °C for 1 h. Dry THF (15 mL) and HMPA (1.1 mL, 6.3 mmol) were added at –78 °C followed by TEMPO **1-2** (187 mg, 1.2 mmol) as a solid and the reaction mixture was stirred for 10 min. $FeCp_2PF_6$ **1-3** was added in small portions with vigorous stirring at –78 °C. Each portion was added after consumption of the previous as monitored by the disappearence of the blue colour (340 mg of **1-3** was added in 5-10 min until the reaction mixture remained blue and inhomogeneous. Two additional spatula tips of **1-3** were added subsequently, total 580 mg (1.7 mmol). After the addition was complete, the reaction mixture was stirred at –75 - –65 °C for 20 min.

Workup and isolation: The reaction mixture was quenched with 6-7 drops of water, diluted with diethyl ether and warmed to r.t. It was filtered through a pad of silica, which was washed with diethyl ether (200 mL). Most of the solvent was evaporated and the remaining material was preadsorbed on silica gel and purified via flash chromatography (hexane/ethyl acetate, gradient 50:1, 20:1, 10:1, 5:1 and 2:1). Ferrocene eluted first at a polarity 50:1 hexane/ethyl acetate. The products eluted starting from polarity 10:1 in the following order: **4-11a,b** + **4-48a,b**+**4-47a,b**+**4-46a,b** , then **4-45a,b** and finally **4-7a,b,** both as diastereomeric mixtures in 15-position. The fractions containing diastereomeric **4-45a,b** and **4-7a,b** were further enriched by another flash chromatography. For yields and ratios, see Tables 4.9 and 4.10.

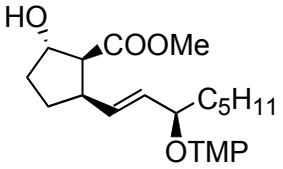
Methyl 2-hydroxy-5-[(*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylates: IR (Film): $\tilde{\nu}$ = 3434 (w), 2930 (s), 2969 (m), 1734 (s), 1461 (m), 1437 (m), 1375 (m), 1359 (m), 1259 (w), 1242 (w), 1199 (m), 1176 (m), 1134 (m), 1044 (w), 1019 (w), 973 (s), 957 (s), 712 (w).

(*1S*,2S*,5R)-Methyl 2-hydroxy-5-[(*1E, 3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-7a:**



^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH_2CH_3), 1.02-1.19 (m, 12H, $NC(CH_3)_2$), 1.21-1.59 (m, 13H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$, $CH_2CHOTMP$), 1.60-1.75 (m, 3H, $CH_2CHOTMP$, CH_2CH_2CHOH), 2.02 (m, 1H, CH_2CH_2CHOH), 2.22 (m, 1H, CH_2CHOH), 2.81 (dd, *J* = 8.5, 6.7 Hz, 1H, $CHCOOMe$), 3.06 (m, 1H, $CHCH$=), 3.64 (s, 3H, $COOCH_3$), 3.93 (dt, *J* = 4.6, 8.4 Hz, 1H, $CHOTMP$), 4.57 (m, 1H, $CHOH$), 5.28 (dd, *J* = 15.3, 8.6 Hz, 1H, CH=CHCHOTMP), 5.38 (m, 1H, =CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 14.1 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.2 (q, $NC(CH_3)_2$), 20.4 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.0 (t, $CH_2CH_2CH_3CH_3$), 29.1 (t, CH_2CH_2CHOH), 32.0 (t, $CH_2CH_2CH_3$), 32.8 (t, CH_2CHOH), 33.9 (q, $NC(CH_3)_2$), 34.5 (t, $TMPOCHCH_2$), 35.4 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 43.5 (d, $CHCHCH$=), 51.4 (q, $COOCH_3$), 57.2 (d, $CHCOOMe$), 58.9 (s, $NC(CH_3)_2$), 59.2 (s, $NC(CH_3)_2$), 74.4 (d, $CHOH$), 84.8 (d, $CHOTMP$), 130.9 (d, CH=CHCHOTMP), 134.6 (d, =CHCHOTMP), 173.4 (s, C=O).

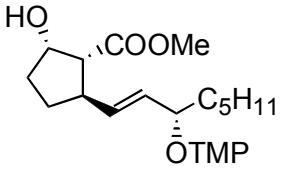
(*1S*,2S*,5R)-Methyl 2-hydroxy-5-[(*1E, 3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-7a:**



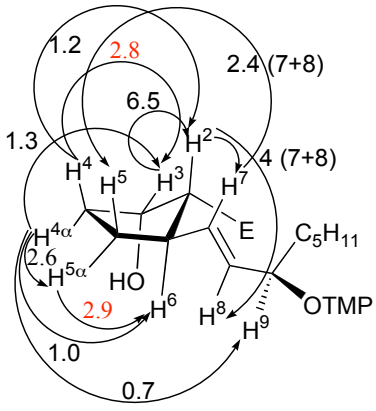
^{1}H NMR (400 MHz): δ = 0.89 (m, 3H, CH_2CH_3), 1.04-1.17 (m, 12H, $NC(CH_3)_2$), 1.19-1.34 (m, 7H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.35-1.59 (m, 6H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$), 1.59-1.73 (m, 3H, $CH_2CHOTMP$, CH_2CH_2CHOH), 1.97 (m, 1H, CH_2CH_2CHOH), 2.20 (m, 1H, CH_2CHOH), 2.82 (dd, *J* = 8.4, 5.9 Hz, 1H, $CHCOOMe$), 3.07 (m, 1H, $CHCHCHOH$), 3.67 (s, 3H, $COOCH_3$), 3.99 (m, 1H, $CHOTMP$), 4.57 (m, 1H, $CHOH$), 5.35 (dd, *J* = 15.4, 7.0 Hz, 1H, CH=CHCHOTMP), 5.42 (dd, *J* = 15.5, 7.5 Hz,

=C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.2 (t, $NCCH_2CH_2CH_2CN$), 20.2 (q, $NC(CH_3)_2$), 20.4 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.1 (t, $CH_2CH_2CH_3CH_3$), 29.2 (t, CH_2CH_2CHOH), 31.9 (t, $CH_2CH_2CH_3$), 33.0 (t, CH_2CHOH), 34.3 (t, TMPOCHCH_2), 34.9 (q, $NC(CH_3)_2$), 35.2 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 43.2 (d, $CH_2CHCH{=}CH$), 51.4 (q, $COOCH_3$), 57.0 (d, CHCOOMe), 58.9 (s, $NC(CH_3)_2$), 60.0 (s, $NC(CH_3)_2$), 74.7 (d, CHOH), 84.6 (d, CHOTMP), 130.5 (d, =CHCHOTMP), 134.0 (d, CH=CHCHOTMP), 173.5 (s, C=O).

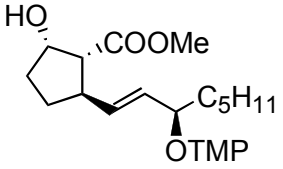
(*1R*,2S*,5R)-Methyl 2-hydroxy-5-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-45a:**



^{1}H NMR (400 MHz): δ = 0.87 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.03 (br. s, 6H, $NC(CH_3)_2$), 1.10 (br. s, 3H, $NC(CH_3)_2$), 1.15 (br. s, 3H, $NC(CH_3)_2$), 1.22-1.35 (m, 8H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.41-1.63 (m, 6H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$, $CH^{\beta}HCH_2CHOH$), 1.68 (m, 1H, $CH_2CHOTMP$), 1.76 (m, 1H, $CH^{\alpha}HCHOH$), 1.98 (m, 1H, $CH^{\beta}HCHOH$), 2.10 (m, 1H, $CH^{\alpha}HCH_2CHOH$), 2.55 (dd, *J* = 10.6, 5.0 Hz, 1H, CHCOOMe), 3.08 (m, 1H, CHCHCHOH), 3.71 (s, 3H, $COOCH_3$), 3.99 (m, 1H, CHOTMP), 4.46 (dt, *J* = 2.9, 5.1 Hz, 1H, CHOH), 5.42 (m, 2H, CH=CH). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.2 (q, $NC(CH_3)_2$), 20.4 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.0 (t, $CH_2CH_2CH_2CH_3$), 29.9 (t, CH_2CH_2CHOH), 31.8 (t, $CH_2CH_2CH_3$), 33.8 (q, $NC(CH_3)_2$), 33.9 (t, CH_2CHOH), 34.4 (t, TMPOCHCH_2), 35.2 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 43.5 (d, CHCHCH=), 51.8 (q, $COOCH_3$), 55.3 (d, CHCOOMe), 58.9 (s, $NC(CH_3)_2$), 60.0 (s, $NC(CH_3)_2$), 74.3 (d, CHOH), 85.0 (d, CHOTMP), 132.9 (d, CH=CH), 133.2 (d, CH=CH), 174.6 (s, C=O). - Significant NOE enhancements:

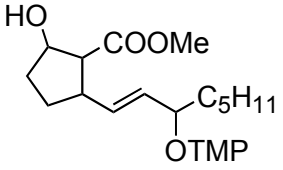


(*1R*,2S*,5R)-Methyl 2-hydroxy-5-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-45a:**



^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH_2CH_3), 1.03 (br. s, 6H, $NC(CH_3)_2$), 1.10 (br. s, 3H, $NC(CH_3)_2$), 1.15 (br. s, 3H, $NC(CH_3)_2$), 1.23-1.40 (m, 7H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.41-1.61 (m, 7H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$, $CH^{\beta}HCH_2CHOH$), 1.67 (m, 1H, $CH_2CHOTMP$), 1.77 (m, 1H, $CH^{\alpha}HCHOH$), 1.95 (m, 1H, $CH^{\beta}HCHOH$), 2.13 (m, 1H, $CH^{\alpha}HCH_2CHOH$), 2.48 (dd, *J* = 11.0, 4.6 Hz, 1H, CHCOOMe), 3.07 (m, 1H, CHCHCHOH), 3.69 (s, 3H, $COOCH_3$), 4.03 (m, 1H, CHOTMP), 4.45 (m, 1H, CHOH), 5.39 (m, 2H, CH=CH). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.2 (q, $NC(CH_3)_2$), 20.4 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.0 (t, $CH_2CH_2CH_3CH_3$), 29.6 (t, CH_2CH_2CHOH), 31.9 (t, $CH_2CH_2CH_3$), 33.9 (t, CH_2CHOH), 34.0 (q, $NC(CH_3)_2$), 34.3 (t, $CH_2CHOTMP$), 35.3 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 44.1 (d, CHCHCH=), 51.6 (q, $COOCH_3$), 55.3 (d, CHCOOMe), 58.8 (s, $NC(CH_3)_2$), 60.1 (s, $NC(CH_3)_2$), 74.1 (d, CHOH), 85.0 (d, CHOTMP), 133.1 (d, CH=CH), 133.7 (d, CH=CH), 174.8 (s, C=O).

Methyl 2-hydroxy-3-[(*1E,3S* and R)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α- and β-4-46a:**



4-46a-I5: ^{1}H NMR (400 MHz): δ = 0.89 (m, 3H, CH_2CH_3), 1.03-1.52 (m, 25H, $NC(CH_3)_2$, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.68-1.94 (m, 6H, CH_2CH_2CHOH, $CH_2CHOTMP$), 2.89 (dd, *J* = 8.7, 4.3 Hz, 1H, CHCOOMe), 2.95 (m, 1H, CHCHCHOH), 3.74 (s, 3H, $COOCH_3$), 4.01 (m, 1H, CHOTMP), 4.43 (m, 1H, CHOH), 5.40 (dd, *J* = 15.4, 8.1, 1H, =CHCHOTMP), 5.53 (dd, *J* = 15.4, 8.2 Hz, 1H, CH=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH_2CH_3), 17.2 (t, $NCCH_2CH_2CH_2CN$), 20.3 (q, $NC(CH_3)_2$), 22.5 (t, CH_2CH_3), 25.1 (t, $CH_2CH_2CH_3CH_3$), 29.9 (t, CH_2CH_2CHOH), 31.9 (t, $CH_2CH_2CH_3$), 33.3 (t, CH_2CHOH), 33.4 (q, $NC(CH_3)_2$), 34.1 (q, $NC(CH_3)_2$), 34.3 (t, $CH_2CHOTMP$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 43.4 (d, CHCHCH=), 51.4 (q, $COOCH_3$), 52.8 (d, CHCOOMe), 73.8 (d,

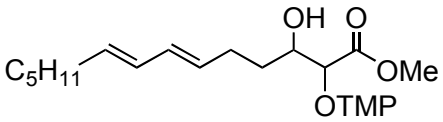
*C*HOH), 84.2 (d, *C*HOTMP), 132.5 (d, *C*H=CHCHOTMP), 133.5 (d, =*C*HCHOTMP), 174.2 (s, C=O).

4-46a-I6: ^{1}H NMR (400 MHz): δ = 0.89 (m, 3H, CH_2CH_3), 1.01-1.69 (m, 26H, $NC(CH_3)_2$, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.76 (m, 1H, CH_2CHOH), 1.82-1.98 (m, 3H, CH_2CHOH, CH_2CH_2CHOH), 2.82 (dd, *J* = 9.0, 4.1 Hz, 1H, C*H*COOMe), 2.98 (m, 1H, C*H*CHCHOH), 3.66 (s, 3H, $COOCH_3$), 3.85 (br. s, 1H, O*H*), 3.95 (dt, *J* = 8.4, 4.7 Hz, 1H, C*H*OTMP), 4.43 (m, 1H, C*H*OH), 5.31 (dd, *J* = 15.2, 8.6, 1H, =C*H*CHOTMP), 5.53 (m, 1H, C*H*=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.3 (q, $NC(CH_3)_2$), 20.4 (q, $NC(CH_3)_2$), 22.5 (t, CH_2CH_3), 25.0 (t, $CH_2CH_2CH_3CH_3$), 29.9 (t, CH_2CH_2CHOH), 32.1 (t, $CH_2CH_2CH_3$), 33.5 (t, CH_2CHOH), 33.9 (q, $NC(CH_3)_2$), 34.6 (t, $TMPOCHCH_2$), 35.3 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 43.7 (d, CHCHCH=), 51.4 (q, $COOCH_3$), 53.2 (d, CHCOOMe), 60.0 (s, $NC(CH_3)_2$), 60.3 (s, $NC(CH_3)_2$), 73.7 (d, CHOH), 84.6 (d, CHOTMP), 133.5 (d, CH=CH), 133.9 (d, CH=CH), 174.3 (s, C=O).

Assignable resonances of **4-46a-I7**: ^{1}H NMR (400 MHz): δ = 2.51 (m, 1H, C*H*COOMe), 2.72 (m, 1H, CHC*H*CH=), 3.68 (s, 3H, $COOCH_3$), 4.40 (m, 1H, C*H*OH). - ^{13}C NMR (100 MHz): δ = 45.1 (d, CHCHCH=), 51.5 (q, $COOCH_3$), 76.5 (d, CHOH), 133.1 (d, CH=), 133.4 (d, =CH), 174.8 (s, C=O).

Assignable resonances of **4-46a-I8**: ^{1}H NMR (400 MHz): δ = 2.52 (m, 1H, C*H*COOMe), 3.70 (s, 3H, $COOCH_3$), 3.99 (m, 1H, C*H*OTMP), 4.39 (m, 1H, C*H*OH). - ^{13}C NMR (100 MHz): δ = 29.8 (t, CH_2CH_2CHOH), 31.8 (t, $CH_2CH_2CH_3$), 33.6 (t, CH_2CHOH), 34.4 (t, $CH_2CHOTMP$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 44.6 (d, CHCHCH=), 51.8 (q, $COOCH_3$), 59.1 (d, CHCOOMe), 76.8 (d, CHOH), 84.9 (d, CHOTMP), 132.9 (d, CH=CH), 133.1 (d, CH=CH), 174.9 (s, C=O).

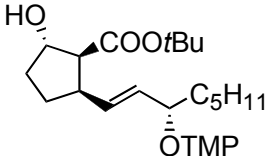
***(6E,8E)*-Methyl 3-hydroxy-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)tetradeca-6,8-dienoate 4-48a:**



^{1}H NMR (400 MHz): δ = 0.89 (m, 3H, CH_2CH_3), 1.01-1.69 (m, 26H, $NC(CH_3)_2$, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$, CH_2CHOH), 2.04 (m, 2H, CH_2CH_2CH=), 2.15 (m, 1H, CH_2CH_2CHOH), 2.29 (m, 1H, CH_2CH_2CHOH), 2.46 (m, 1H, O*H*), 3.74 (s, COO*Me*),

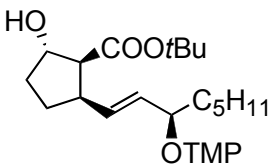
4.16 (dt, *J* = 8.7, 4.3 Hz, 1H, C*H*OH), 4.27 (d, *J* = 3.9 Hz, 1H, C*H*OTMP), 5.57 (m, 2H, C*H*=CHCH=C*H*), 6.00 (m, 2H, CH=C*H*C*H*=CH). - ^{13}C NMR (100 MHz): δ = 14.1 (q, CH_2CH_3), 17.0 (t, $NCCH_2CH_2CH_2CN$), 20.3 (q, $NC(CH_3)_2$), 20.7 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 28.8 (t, CH_2CH_2CHOH), 29.0 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $CH_2CH_2CH_3$), 32.5 (t, $=CHCH_2(CH_2)_3$), 32.8 (t, CH_2CHOH), 33.9 (q, $NC(CH_3)_2$), 34.5 (q, $NC(CH_3)_2$), 40.3 (t, $NCCH_2CH_2CH_2CN$), 51.5 (q, $COOCH_3$), 60.0 (s, $NC(CH_3)_2$), 60.3 (s, $NC(CH_3)_2$), 71.1 (d, *C*HOH), 87.1 (d, *C*HOTMP), 130.0 (d, =*C*H), 130.7 (d, *C*H=), 131.2 (d, =*C*H), 133.1 (d, =*C*H), 171.6 (s, C=O).

(*1S*,2S*,5R)-*tert*-Butyl 2-hydroxy-5-[(*1E*,3*S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-7b:**



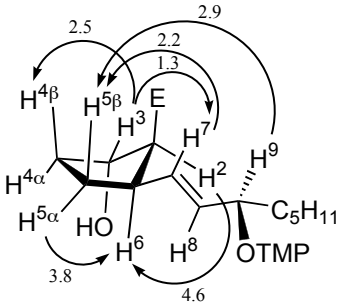
^{1}H NMR (400 MHz): δ = 0.83 (m, 3H, CH_2CH_3), 1.02-1.08 (m, 12H, $NC(CH_3)_2$), 1.18-1.58 (m, 13H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_3$, $CH_2CHOTMP$), 1.40 (s, 9H, $C(CH_3)_3$), 1.55 (m, 1H, CH_2CHOH), 1.64 (m, 2H, CH_2CH_2CHOH, $CH_2CHOTMP$), 1.93 (m, 1H, CH_2CH_2CHOH), 2.16 (m, 1H, CH_2CHOH), 2.65 (dd, *J* = 8.1, 6.2 Hz, 1H, C*H*COO*t*Bu), 2.97 (m, 1H, CH_2CHCH=), 3.96 (dt, *J* = 5.1, 7.6 Hz, 1H, C*H*OTMP), 4.46 (dd, *J* = 13.3, 6.2 Hz, 1H, C*H*OH), 5.34 (dd, *J* = 15.3, 7.2 Hz, 1H, C*H*=CHCHOTMP), 5.40 (dd, *J* = 15.4, 7.2 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH_2CH_3), 17.2 (t, $NCCH_2CH_2CH_2CN$), 20.2 (q, $NC(CH_3)_2$), 20.4 (q, $NC(CH_3)_2$), 22.46 (t, CH_2CH_3), 25.0 (t, $CH_2CH_2CH_2CH_3$), 28.0 (q, $C(CH_3)_3$), 29.0 (t, CH_2CH_2CHOH), 32.0 (t, $CH_2CH_2CH_3$), 32.5 (t, CH_2CHOH), 33.9 (q, $NC(CH_3)_2$), 34.6 (t, $CH_2CHOTMP$), 34.9 (q, $NC(CH_3)_2$), 40.1 (t, $NCCH_2CH_2CH_2CN$), 43.3 (d, CH_2CHCH=), 58.1 (d, *C*HCOO*t*Bu), 58.9 (s, $NC(CH_3)_2$), 74.5 (d, *C*HOH), 80.5 (s, $C(CH_3)_3$), 84.55 (d, *C*HOTMP), 131.1 (d, *C*H=CHCHOTMP), 134.0 (d, =*C*HCHOTMP), 172.3 (s, C=O).

(*1S*,2S*,5R)-*tert*-Butyl 2-hydroxy-5-[(*R*,E)*-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-7b:**

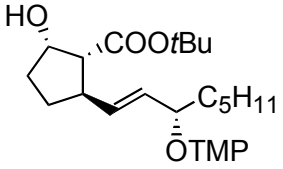


^{1}H NMR (400 MHz): δ = 0.83 (m, 3H, CH_2CH_3), 1.02-1.08 (m, 12H, $NC(CH_3)_2$), 1.18-1.58 (m, 13H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$, $CH_2CHOTMP$), 1.43 (s, 9H, $C(CH_3)_3$),

1.55 (m, 1H, C*H*$_2$CHOH), 1.64 (m, 2H, C*H*$_2$CH$_2$CHOH, C*H*$_2$CHOTMP), 1.93 (m, 1H, C*H*$_2$CH$_2$CHOH), 2.16 (m, 1H, C*H*$_2$CHOH), 2.66 (dd, *J* = 8.0, 5.7 Hz, 1H, C*H*COO*t*Bu), 2.99 (m, 1H, CH$_2$C*H*CH=), 3.96 (m, 1H, C*H*OTMP), 4.43 (dd, *J* = 12.9, 5.7 Hz, 1H, C*H*OH), 5.40 (m, 2H, C*H*=C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.48 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 28.1 (q, C(*C*H$_3$)$_3$), 29.1 (t, *C*H$_2$CH$_2$CHOH), 31.8 (t, *C*H$_2$CH$_2$CH$_3$), 32.7 (t, *C*H$_2$CHOH), 33.9 (q, NC(*C*H$_3$)$_2$), 34.1 (t, *C*H$_2$CHOTMP), 34.9 (q, NC(*C*H$_3$)$_2$), 40.1 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.0 (d, CH$_2$*C*HCH=), 57.8 (d, *C*HCOO*t*Bu), 58.9 (s, N*C*(CH$_3$)$_2$), 74.8 (d, *C*HOH), 80.6 (s, *C*(CH$_3$)$_3$), 84.48 (d, *C*HOTMP), 130.7 (d, *C*H=), 133.8 (d, =*C*H), 172.4 (s, C=O). Significant NOE enhancements:

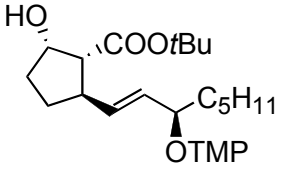


(*1R*,2S*,5R)-*tert*-Butyl 2-hydroxy-5-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-45b:**



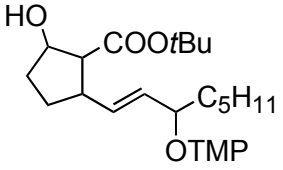
^{1}H NMR (400 MHz): δ = 0.83 (t, *J* = 6.8 Hz, 3H, CH$_2$C*H*$_3$), 1.10-1.12 (m, 12H, NC(C*H*$_3$)$_2$), 1.15-1.30 (m, 7H, NCCH$_2$C*H*$_2$CH$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.30-1.60 (m, 7H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$CHOTMP, C*H*$_2$CHOH), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.71 (m, 2H, C*H*$_2$CHOTMP, C*H*$_2$CH$_2$CHOH), 1.86 (m, 1H, C*H*$_2$CH$_2$CHOH), 2.06 (m, 1H, C*H*$_2$CHOH), 2.41 (dd, *J* = 10.3, 4.9 Hz, 1H, C*H*COO*t*Bu), 3.07 (m, 1H, CH$_2$C*H*CH=), 3.98 (m, 1H, C*H*OTMP), 4.38 (m, 1H, C*H*OH), 5.40 (dd, *J* = 15.6, 7.3 Hz, 1H, C*H*=CHCHOTMP), 5.47 (dd, *J* = 15.5, 6.0 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 13.8 (q, CH$_2$*C*H$_3$), 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.3 (q, NC(*C*H$_3$)$_2$), 22.4 (t, *C*H$_2$CH$_3$), 25.0 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 28.00 (q, OC(*C*H$_3$)$_3$), 29.5 (t, *C*H$_2$CHOH), 31.7 (t, *C*H$_2$CH$_2$CH$_3$), 33.6 (t, *C*H$_2$CH$_2$CHOH), 33.9 (q, NC(*C*H$_3$)$_2$), 34.1 (t, *C*H$_2$CHOTMP), 35.1 (q, NC(*C*H$_3$)$_2$), 40.0 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.9 (d, CH$_2$*C*HCH=), 55.6 (d, *C*HCOO*t*Bu), 58.9 (s, N*C*(CH$_3$)$_2$), 59.7 (s, N*C*(CH$_3$)$_2$), 74.2 (d, *C*HOH), 81.1 (s, *C*(CH$_3$)$_3$), 84.6 (d, *C*HOTMP), 132.1 (d, *C*H=CHCHOTMP), 133.1 (d, =*C*HCHOTMP), 173.5 (s, C=O).

(*1R*,2S*,5R)-*tert*-Butyl 2-hydroxy-5-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-45b:**



^{1}H NMR (400 MHz): δ = 0.83 (t, *J* = 6.8, 3H, CH_2CH_3), 1.10-1.12 (m, 12H, $NC(CH_3)_2$), 1.15-1.30 (m, 7H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.30-1.60 (m, 7H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$, CH_2CHOH), 1.43 (s, 9H, $C(CH_3)_3$), 1.71 (m, 2H, $CH_2CHOTMP$, CH_2CH_2CHOH), 1.86 (m, 1H, CH_2CH_2CHOH), 2.06 (m, 1H, CH_2CHOH), 2.33 (dd, *J* = 10.6, 4.7 Hz, 1H, $CHCOOtBu$), 3.07 (m, 1H, CH_2CHCH=), 3.98 (m, 1H, $CHOTMP$), 4.38 (m, 1H, $CHOH$), 5.37 (m, 2H, CH=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH_2CH_3), 17.1 (t, $NCCH_2CH_2CH_2CN$), 20.3 (q, $NC(CH_3)_2$), 22.4 (t, CH_2CH_3), 24.9 (t, $CH_2CH_2CH_2CH_3$), 27.97 (q, $OC(CH_3)_3$), 29.4 (t, CH_2CHOH), 31.8 (t, $CH_2CH_2CH_3$), 33.7 (t, CH_2CH_2CHOH), 33.9 (q, $NC(CH_3)_2$), 34.4 (t, $CH_2CHOTMP$), 35.1 (q, $NC(CH_3)_2$), 40.1 (t, $NCCH_2CH_2CH_2CN$), 43.7 (d, CH_2CHCH=), 55.9 (d, $CHCOOtBu$), 58.9 (s, $NC(CH_3)_2$), 59.7 (s, $NC(CH_3)_2$), 74.1 (d, $CHOH$), 81.1 (s, $C(CH_3)_3$), 84.7 (d, $CHOTMP$), 133.0 (d, CH=CHCHOTMP), 133.5 (d, =CHCHOTMP), 173.6 (s, C=O).

***tert*-Butyl 2-hydroxy-5-[(*1E,S* and R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α- and β-4-46b:**



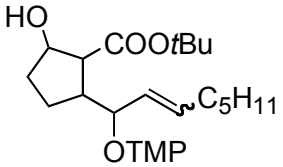
Assignable resonances of **4-46b-I3-1**: ^{1}H NMR (400 MHz): δ = 1.27-1.58 (m, 6H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$), 1.64 (m, 3H, $CH_2CHOTMP$, CH_2CH_2CHOH), 1.83 (m, 1H, CH_2CH_2CHOH), 1.93 (m, 1H, CH_2CHOH), 2.37 (dd, *J* = 9.5, 6.5 Hz, 1H, $CHCOOtBu$), 2.71 (m, 1H, CH_2CHCH=), 3.96 (m, 1H, $CHOTMP$), 4.30 (m, 1H, $CHOH$), 5.48 (dd, *J* = 15.6, 6.6 Hz, 1H, CH=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 29.4 (t, CH_2CH_2CHOH), 31.8 (t, $CH_2CH_2CH_3$), 33.4 (t, CH_2CHOH), 34.3 (t, $CH_2CHOTMP$), 43.7 (d, CH_2CHCH=), 59.8 (d, $CHCOOtBu$), 76.5 (d, $CHOH$), 84.8 (d, $CHOTMP$), 132.3 (d, =CHCHOTMP), 133.3 (d, CH=CHCHOTMP), 170.2 (s, C=O).

Assignable resonances of **4-46b-I3-2**: ^{1}H NMR (400 MHz): δ = 1.67 (m, 3H, C*H*$_2$CHOTMP, C*H*$_2$C*H*$_2$CHOH), 1.87 (m, 1H, C*H*$_2$CH$_2$CHOH), 1.99 (m, 1H, C*H*$_2$CHOH), 2.36 (dd, *J* = 9.8, 6.6 Hz, 1H, C*H*COO*t*Bu), 2.74 (m, 1H, CH$_2$C*H*CH=), 3.99 (m, 1H, C*H*OTMP), 4.34 (m, 1H, C*H*OH), 5.52 (dd, *J* = 15.5, 6.6 Hz, 1H, C*H*=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 22.5 (d, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 28.1 (q, C(*C*H$_3$)$_3$), 29.2 (t, *C*H$_2$CH$_2$CHOH), 31.9 (d, *C*H$_2$CH$_2$CH$_3$), 33.4 (t, *C*H$_2$CHOH), 34.4 (d, *C*H$_2$CHOTMP), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 44.7 (d, CH$_2$*C*HCH=), 60.2 (d, *C*HCOO*t*Bu), 76.5 (d, *C*HOH), 80.5 (s, *C*(CH$_3$)$_3$), 84.9 (d, *C*HOTMP), 133.0 (d, =*C*HCHOTMP), 133.7 (d, *C*H=CHCHOTMP).

4-46b-I4-1: ^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH$_2$C*H*$_3$), 1.03-1.17 (m, 12H, NC(C*H*$_3$)$_2$), 1.26-1.58 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$CHOTMP), 1.45 or 1.47 (s, 9H, C(C*H*$_3$)$_3$), 1.60 (m, 1H, C*H*$_2$CHOTMP), 1.82-1.89 (m, 4H, C*H*$_2$C*H*$_2$CHOH), 2.70 (dd, *J* = 8.4, 4.4 Hz, 1H, C*H*COO*t*Bu), 2.91 (m, 1H, CH$_2$C*H*CH=), 4.02 (ddd, *J* = 8.5, 6.8, 5.5 Hz, 1H, C*H*OTMP), 4.40 (m, 1H, C*H*OH), 5.37 (dd, *J* = 15.3, 8.7 Hz, 1H, =C*H*CHOTMP), 5.63 (dd, *J* = 15.3, 9.0 Hz, 1H, C*H*=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.5 (q, NC(*C*H$_3$)$_2$), 22.4 (t, *C*H$_2$CH$_3$), 24.9 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 28.0 or 28.2 (q, OC(*C*H$_3$)$_3$), 29.8 (t, *C*H$_2$CH$_2$CHOH), 31.3 (t, *C*H$_2$CH$_2$CH$_3$), 33.2 (t, *C*H$_2$CHOH), 33.9 (q, NC(*C*H$_3$)$_2$), 34.7 (t, *C*H$_2$CHOTMP), 34.8 (q, NC(*C*H$_3$)$_2$), 40.1 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.8 (d, CH$_2$*C*HCH=), 53.6 (d, *C*HCOO*t*Bu), 58.8 (s, N*C*(CH$_3$)$_2$), 60.5 (s, N*C*(CH$_3$)$_2$), 73.7 (d, *C*HOH), 81.2 or 81.7 (s, *C*(CH$_3$)$_3$), 84.2 (d, *C*HOTMP), 133.1 (d, =*C*HCHOTMP), 133.4 (d, *C*H=CHCHOTMP), 173.1 or 174.3 (s, C=O).

Assignable resonances of **4-46b-I4-2**: ^{1}H NMR (400 MHz): δ = 2.81 (dd, *J* = 8.6, 4.6 Hz, 1H, C*H*COO*t*Bu), 2.94 (m, 1H, CH$_2$C*H*CH=), 4.03 (m, 1H, C*H*OTMP), 4.43 (m, 1H, C*H*OH).

***tert*-Butyl 2-hydroxy-5-[(*1S* and R**)-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-2-en-1-yl]cyclopentanecarboxylate 4-47b:**

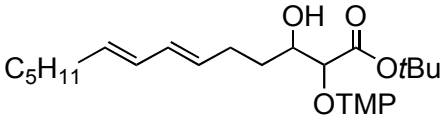


4-47b-CPP1: ^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH$_2$C*H*$_3$), 1.03-1.17 (m, 12H, NC(C*H*$_3$)$_2$), 1.26-1.58 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.45 or 1.47 (s,

9H, C(C*H*$_3$)$_3$), 1.75 (m, 3H, C*H*$_2$C*H*$_2$CHOH), 1.97 (m, 1H, C*H*$_2$CH$_2$CHOH), 2.04 (m, 2H, C*H*$_2$CHOTMP), 2.60 (m, 1H, CH$_2$C*H*CH=), 2.88 (dd, *J* = 9.2, 4.9 Hz, 1H, C*H*COO*t*Bu), 4.26 (m, 1H, C*H*OTMP), 4.40 (m, 1H, C*H*OH), 5.48 (m, 2H, C*H* =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 13.9 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.5 (q, NC(*C*H$_3$)$_2$), 22.4 (t, *C*H$_2$CH$_3$), 24.2 (t, *C*H$_2$CH$_2$CHOH), 28.0 or 28.2 (q, OC(*C*H$_3$)$_3$), 28.6 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 32.0 (t, *C*H$_2$CH$_2$CH$_3$), 32.1 (t, *C*H$_2$CHOTMP), 33.9 (q, NC(*C*H$_3$)$_2$), 34.1 (t, *C*H$_2$CHOH), 34.8 (q, NC(*C*H$_3$)$_2$), 40.1 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 45.1 (d, CH$_2$*C*HCH=), 51.5 (d, *C*HCOO*t*Bu), 58.8 (s, N*C*(CH$_3$)$_2$), 60.5 (s, N*C*(CH$_3$)$_2$), 74.6 (d, *C*HOH), 81.2 or 81.7 (s, *C*(CH$_3$)$_3$), 84.6 (d, *C*HOTMP), 130.8 (d, *C*H=), 133.9 (d, =*C*H), 173.1 or 174.3 (s, C=O).

Assignable resonances of **4-47b-CPP2**: ^{1}H NMR (400 MHz): δ = 2.51 (dd, *J* = 9.6, 4.7 Hz, 1H, C*H*COO*t*Bu), 2.78 (m, 1H, CH$_2$C*H*CH=), 4.16 (dd, *J* = 9.1, 5.3 Hz, 1H, C*H*OTMP), 4.35 (m, 1H, C*H*OH), 5.41 (m, 2H, C*H* =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 24.4 (t, *C*H$_2$CH$_2$CHOH), 28.1 (q, OC(*C*H$_3$)$_3$), 28.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 34.0 (t, *C*H$_2$CHOH), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 44.1 (d, CH$_2$*C*HCH=), 52.1 (d, *C*HCOO*t*Bu), 74.5 (d, *C*HOH), 86.6 (d, *C*HOTMP), 129.2 (d, *C*H=), 135.1 (d, =*C*H), 174.6 (s, C=O).

***(6E,8E)*-*tert*-Butyl 3-hydroxy-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)tetradeca-6,8-dienoate 4-48b:**



^{1}H NMR (400 MHz): δ = 0.88 (m, 3H, CH$_2$C*H*$_3$), 1.45 (m, 12H, NC(C*H*$_3$)$_2$), 1.26-1.49 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.49 (s, 9H, OC(C*H*$_3$)$_3$), 1.54 (m, 2H, C*H*$_2$CHOH), 2.04 (q, *J* = 7.2 Hz, 2H, CH$_2$CH$_2$C*H*$_2$CH=), 2.14 (m, 1H, C*H*$_2$CH$_2$CHOH), 2.26 (m, 1H, C*H*$_2$CH$_2$CHOH), 2.58 (m, 1H, O*H*), 4.14 (m, 1H, C*H*OTMP), 4.17 (m, 1H, C*H*OH), 5.55 (m, 2H, C*H*=CHCH=C*H*), 6.01 (m, 2H, CH=C*H*C*H*=CH). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH$_2$*C*H$_3$), 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.1 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 28.1 (q, C(*C*H$_3$)$_3$), 28.8 (t, *C*H$_2$CH$_2$CHOH), 29.0 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.4 (t, *C*H$_2$CH$_2$CH$_3$), 32.5 (t, =CH*C*H$_2$CH$_2$CH$_2$), 32.8 (q, NC(*C*H$_3$)$_2$), 33.0 (t, *C*H$_2$CHOH), 33.3 (q, NC(*C*H$_3$)$_2$), 40.4 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 60.0 (s, N*C*(CH$_3$)$_2$), 71.5 (d, *C*HOH), 81.8 (s, *C*(CH$_3$)$_3$), 87.1 (d, *C*HOTMP), 130.1 (d, =*C*H), 130.8 (d, =*C*HCH$_2$CH$_2$CHOH), 131.1 (d, =*C*H), 132.9 (d, (CH$_2$)$_4$*C*H=), 170.2 (s, C=O).

Table 6.4 Significant NMR data of compounds 15α,β-**4-7a,b** and 15α,β-**4-45a,b**

^{1}H NMR	H8	H9	H12	H13	H14	H15
15α-**4-7b**	2.65 (dd)	4.46 (dd)	2.97 (m)	5.34 (m)	5.40 (m)	3.96 (dt)
15β-**4-7b**	2.66 (dd)	4.43 (dd)	2.99 (m)	5.40 (m)	5.40 (m)	3.96 (m)
15α-**4-7a**	2.82 (dd)	4.57 (m)	3.07 (m)	5.35 (dd)	5.42 (dd)	3.99 (m)
15β-**4-7a**	2.81 (dd)	4.57 (m)	3.06 (m)	5.28 (dd)	5.38 (m)	3.93 (dt)
15α-**4-45b**	2.41 (dd)	4.38 (dd)	3.07 (m)	5.47 (dd)	5.40 (dd)	3.98 (m)
15β-**4-45b**	2.33 (dd)	4.38 (m)	3.07 (m)	5.37 (m)	5.37 (m)	3.98 (m)
15α-**4-45a**	2.55 (dd)	4.46 (dt)	3.08 (m)	5.42 (m)	5.42 (m)	3.99 (m)
15β-**4-45a**	2.48 (dd)	4.45 (m)	3.07 (m)	5.39 (m)	5.39 (m)	4.03 (m)
^{13}C NMR	C8	C9	C12	C13	C14	C15
15α-**4-7b**	58.1 (d)	74.5 (d)	43.3 (d)	131.1 (d)	134.0 (d)	84.5 (d)
15β-**4-7b**	57.8 (d)	74.8 (d)	43.0 (d)	130.7 (d), 133.8 (d)		84.5 (d)
15β-**4-7a**	57.0 (d)	74.7 (d)	43.2 (d)	130.5 (d), 134.0 (d)		84.6 (d)
15α-**4-7a**	57.2 (d)	74.4 (d)	43.5 (d)	130.9 (d)	134.6 (d)	84.8 (d)
15α-**4-45b**	55.6 (d)	74.2 (d)	42.9 (d)	132.1 (d)	133.1 (d)	84.6 (d)
15β-**4-45b**	55.9 (d)	74.1 (d)	43.7 (d)	133.0 (d)	133.5 (d)	84.7 (d)
15α-**4-45a**	55.3 (d)	74.3 (d)	43.5 (d)	132.9 (d), 133.2 (d)		85.0 (d)
15β-**4-45a**	55.3 (d)	74.1 (d)	44.1 (d)	133.1 (d), 133.7 (d)		85.0 (d)

Oxidative cyclisations of dianions of 3,5-dioxygenated esters 4-12 (General procedures):

Procedure A: Anhydrous LiCl (193 mg, 4.5 mmol) was dried by heating in vacuum under stirring 3-5 times for 3 min at 10 min intervals. It was dissolved in 18 mL dry THF under nitrogen and *i*Pr$_2$NH (0.230 mL, 1.62 mmol) and BuLi (1.01 mL, 1.6*M* in hexane, 1.62 mmol) were added subsequently at –78 °C. The resulting mixture was stirred for 30 min. Esters **4-12a,b** (0.65 mmol) dissolved in 1 mL of dry THF were added dropwise to the LDA solution at –78 °C. The vial was rinsed with 1 mL THF. The mixture was warmed from –78 to –40 °C in 1 h, and stirred at –40 °C for 20 min. After cooling to –78 °C, 0.68 mL (3.9 mmol) HMPA was added dropwise followed by addition of 122 mg (0.78 mmol) TEMPO **1-2** as a solid. The mixture was stirred at –78 °C for 5 min and $FeCp_2PF_6$ **1-3** was added in small portions with vigorous stirring. Each portion was added after consumption of the previous as monitored by the disappearence of the blue colour (About 300 mg of **1-3** were added in 10 min, when the reaction mixture remained blue and inhomogeneous. Two additional spatula tips of **1-3** were added subsequently, total 540 mg). After the addition was complete, the reaction mixture was stirred at –78 - –65 °C for 20 min.

Procedure B: *i*Pr_2NH (0.62 mL, 4.4 mmol) was added under nitrogen to a solution of LiCl (524 mg, 12.3 mmol, dried as described above) in 45 mL dry THF, and the mixture was cooled to –78 °C. BuLi (2.75 mL, 4.4 mmol, 1.6*M* in hexane) was added. After stirring for 0.5 h, esters **4-12a,b** (1.76 mmol) dissolved in 5 mL dry THF were added to the LDA solution at –78 °C. The mixture was warmed from –78 to –40 °C in 1 h, and stirred for additional 0.5 h at –40 °C. After cooling to –78 °C HMPA (1.8 mL, 10.6 mmol) was added dropwise followed by addition of solid TEMPO **1-2** (55 mg, 0.35 mmol). The reaction mixture was stirred at –78 °C for 10 min. In the meantime, **1-2** (220 mg, 1.41 mmol) and **1-3** (583 mg, 1.76 mmol) were mixed to homogenity in a vial. This mixture of **1-3** and **1-2** was added in small portions with vigorous stirring. Each portion was added after consumption of the previous as monitored by the disappearence of the blue colour over a period of 13 min. After the addition was complete, the colour did not remain blue, therefore three additional portions of **1-3** (320 mg, 0.97 mmol) were added and the blue inhomogeneous reaction mixture was stirred at –78 - –60 °C for 30 min.

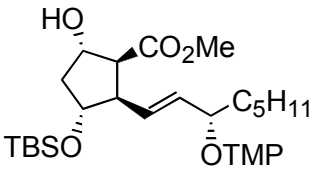
Procedure C: A 20% solution of *t*BuMgCl in THF (0.61 mL, 0.97 mmol) was added via syringe to a solution of esters **4-12a,b** (0.65 mmol) in 5 mL dry THF at –78 °C. The mixture was stirred for 40 min at –78 - –50 °C. After cooling to –78 °C LDA (0.71 mL, 2*M* solution in THF/*n*-heptane, 1.43 mmol) was added and the mixture was stirred at –78 to –40 °C for 1 h. Dry THF (15 mL) and HMPA (0.68 mL, 3.9 mmol) were added at –78 °C followed by solid TEMPO **1-2** (122 mg, 0.78 mmol) and the reaction mixture was stirred for 10 min. $FeCp_2PF_6$ **1-3** was added in small portions with vigorous stirring at –78 °C. Each portion was added after consumption of the previous as monitored by the disappearence of the blue colour (380 mg of **1-3** was added in 5-10 min until the reaction mixture remained blue and inhomogeneous. Two additional spatula tips of **1-3** were added subsequently, total 590 mg (1.8 mmol). After the addition was complete, the reaction mixture was stirred at –75 - –65 °C for 20 min.

Workup and isolation: The reaction mixture was quenched with 7 drops of water, diluted with diethyl ether and allowed to warm to r.t. It was filtered through a pad of silica, which was washed with ether (200 mL). Most of the solvent was evaporated and the remaining material was preadsorbed on silica gel and purified via flash chromatography (hexane/ethyl acetate, gradient 50:1, 20:1, 10:1, 5:1 and 2:1). Ferrocene eluted first at a polarity 50:1 hexane/ethyl acetate. The products eluted starting from polarity 20:1 in the following order: **4-53a,b** + **4-52a,b**, **4-12a,b** + **4-52a,b**, traces of two unkown cyclic products (not always detected), **4-50a,b** and finally **4-8a,b,** both as diastereomeric mixtures in 15-position. The

desired products were isolated and their purity was determined by combustion analysis. The fractions containing diastereomeric **4-50a,b** and **4-8a,b** were further enriched by another flash chromatography. For yields and ratios, see Tables 4.11, 4.12 and 4.13.

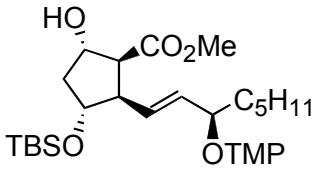
Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*E)*-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylates: IR (Film): $\tilde{\nu}$ = 3441 (w), 2952 (m), 2929 (s), 2857 (m), 1735 (m), 1465 (w), 1437 (w), 1375 (w), 1360 (w), 1254 (m), 1207 (w), 1170 (w), 1130 (m), 1086 (m), 1006 (m), 974 (m), 862 (m), 836 (s), 776 (s), 714 (w). - MS(ESI) *m/z* (%): 1102 (22) [2M+Na^++H], 562 (61) [M+Na^+], 540 (100) [M+H^+], 173 (10). - Combustion analysis: $C_{30}H_{57}NO_5Si$ (539.86): calc. C 66.74, H 10.64, N 2.59; found C 66.72, H 10.60, N 2.54.

(*1S*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-8a:**



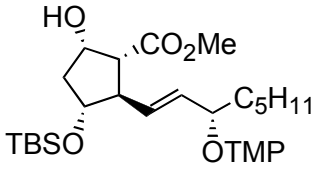
^{1}H NMR (400 MHz): δ = 0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.816 (m, 3H, CH$_2$C*H*$_3$), 0.829 (s, 9H, SiC(C*H*$_3$)$_3$), 0.92-1.05 (m, 12H, NC(C*H*$_3$)$_2$), 1.10-1.27 (m, 7H, NCCH$_2$C*H*$_2$CH$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.28-1.52 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, TMPOCHC*H*$_2$), 1.57 (m, 1H, TMPOCHC*H*$_2$), 1.66 (m, 1H, CHC*H*$_2$CH), 2.28 (m, 1H, CHC*H*$_2$CH), 2.55 (d, *J* = 6.9 Hz, 1H, O*H*), 2.96 (m, 1H, TBSOCHC*H*), 3.18 (dd, *J* = 8.2, 5.0 Hz, 1H, C*H*COOMe), 3.56 (s, 3H, OC*H*$_3$), 3.87 (dt, *J* = 8.3, 4.6 Hz, 1H, C*H*OTMP), 4.08 (m, 1H, C*H*OTBS), 4.52 (m, 1H, C*H*OH), 5.01 (dd, *J* = 15.3, 10.3 Hz, 1H, C*H*=CHCHOTMP), 5.43 (dd, *J* = 15.4, 7.5 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.1 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 24.9 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 32.1 (t, *C*H$_2$CH$_2$CH$_3$), 34.7 (t, TMPOCH*C*H$_2$), 35.0 (q, NC(*C*H$_3$)$_2$), 35.5 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.4 (t, CH*C*H$_2$CH), 51.4 (q, O*C*H$_3$), 54.4 (d, CH*C*HCH=), 56.6 (d, *C*HCOOMe), 60.0 (s, N*C*(CH$_3$)$_2$), 60.1 (s, N*C*(CH$_3$)$_2$), 74.1 (d, *C*HOH), 78.4 (d, *C*HOTBS), 84.7 (d, *C*HOTMP), 127.5 (d, *C*H=CHCHOTMP), 136.9 (d, =*C*HCHOTMP), 173.4 (s, C=O).

(*1S*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-8a:**



^{1}H NMR (400 MHz): δ = –0.004 (s, 3H, Si(C*H*$_3$)$_2$), 0.000 (s, 3H, Si(C*H*$_3$)$_2$), 0.818 (m, 3H, CH$_2$C*H*$_3$), 0.822 (s, 9H, SiC(C*H*$_3$)$_3$), 0.92-1.05 (m, 12H, NC(C*H*$_3$)$_2$), 1.10-1.27 (m, 7H, NCCH$_2$C*H*$_2$CH$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.28-1.52 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, TMPOCHC*H*$_2$), 1.57 (m, 1H, TMPOCHC*H*$_2$), 1.66 (m, 1H, CHC*H*$_2$CH), 2.28 (m, 1H, CHC*H*$_2$CH), 2.54 (d, *J* = 7.4 Hz, 1H, O*H*), 2.96 (m, 1H, TBSOCHC*H*), 3.15 (dd, *J* = 8.4, 4.8 Hz, 1H, C*H*COOMe), 3.61 (s, 3H, OC*H*$_3$), 3.92 (dt, *J* = 8.1, 4.6 Hz, 1H, C*H*OTMP), 4.01 (dt, *J* = 5.1, 2.5 Hz, 1H, C*H*OTBS), 4.47 (m, 1H, C*H*OH), 5.10 (dd, *J* = 15.4, 9.1 Hz, 1H, C*H*=CHCHOTMP), 5.42 (dd, *J* = 15.4, 8.4 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.8 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.77 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 34.1 (q, NC(*C*H$_3$)$_2$), 34.4 (t, TMPOCH*C*H$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.5 (t, CH*C*H$_2$CH), 51.6 (q, O*C*H$_3$), 53.6 (d, CH*C*HCH=), 56.1 (d, *C*HCOOMe), 59.0 (s, N*C*(CH$_3$)$_2$), 59.1 (s, N*C*(CH$_3$)$_2$), 74.1 (d, *C*HOH), 78.6 (d, *C*HOTBS), 84.4 (d, *C*HOTMP), 127.7 (d, *C*H=CHCHOTMP), 136.1 (d, =*C*HCHOTMP), 173.5 (s, C=O).

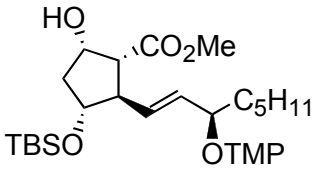
(*1R*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-50a:**



^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.82 (m, 12H, CH$_2$C*H*$_3$, SiC(C*H*$_3$)$_3$), 0.86-1.09 (m, 12H, NC(C*H*$_3$)$_2$), 1.11-1.51 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$CHOTMP), 1.61 (m, 1H, C*H*$_2$CHOTMP), 1.87 (m, 2H, CHC*H*$_2$CH), 2.65 (dd, *J* = 8.3, 5.3 Hz, 1H, C*H*COOMe), 3.18 (m, 1H, TBSOCHC*H*), 3.26 (br. s, 1H, O*H*), 3.65 (s, 3H, OC*H*$_3$), 3.89 (m, 1H, C*H*OTMP), 4.01 (dt, *J* = 4.7, 2.5 Hz, 1H, C*H*OTBS), 4.39 (m, 1H, C*H*OH), 5.22 (dd, *J* = 15.4, 8.3 Hz, 1H, C*H*=CHCHOTMP), 5.38 (dd, *J* = 15.3, 8.7 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –5.0 (q, Si(*C*H$_3$)$_2$), –4.8 (q, Si(*C*H$_3$)$_2$), 13.9 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN),

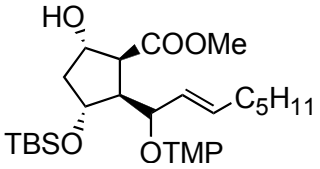
17.8 (s, Si*C*$(CH_3)_3$), 20.1 (q, NC(*C*$H_3)_2$), 20.3 (q, NC(*C*$H_3)_2$), 22.5 (t, *C*H_2CH_3), 25.0 (t, *C*$H_2CH_2CH_2CH_3$), 25.65 (q, SiC(*C*$H_3)_3$), 31.8 (t, *C*$H_2CH_2CH_3$), 33.8 (q, NC(*C*$H_3)_2$), 34.4 (t, TMPOCH*C*H_2), 35.3 (q, NC(*C*$H_3)_2$), 40.1 (t, NC*C*H_2CH_2*C*H_2CN), 43.0 (t, CH*C*H_2CH), 51.7 (q, O*C*H_3), 51.9 (d, CH*C*HCH=), 56.6 (d, *C*HCOOMe), 58.8 (s, N*C*$(CH_3)_2$), 60.1 (s, N*C*$(CH_3)_2$), 75.2 (d, *C*HOH), 79.5 (d, *C*HOTBS), 84.9 (d, *C*HOTMP), 131.2 (d, *C*H=CHCHOTMP), 134.3 (d, =*C*HCHOTMP), 172.1 (s, C=O).

(*1R*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-50a:**



^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3)_2$), 0.03 (s, 3H, Si(C*H*$_3)_2$), 0.79 (m, 3H, CH_2C*H*$_3$), 0.81 (s, 9H, SiC(C*H*$_3)_3$), 0.95-1.05 (m, 12H, NC(C*H*$_3)_2$), 1.11-1.51 (m, 13H, NC*H*$_2$C*H*$_2$C*H*$_2$CN, CH_2C*H*$_2$C*H*$_2$C*H*$_2$$CH_3$, C*H*$_2$CHOTMP), 1.62 (m, 1H, C*H*$_2$CHOTMP), 1.82 (br. d, *J* = 14.3 Hz, 1H, CHC*H*$_2$CH), 1.88 (dt, *J* = 14.0, 4.7 Hz, 1H, CHC*H*$_2$CH), 2.59 (dd, *J* = 8.1, 5.3 Hz, 1H, C*H*COOMe), 3.17 (dt, *J* = <1, 7.9 Hz, 1H, TBSOCHC*H*), 3.31 (br. d, *J* = 9.1 Hz, 1H, O*H*), 3.63 (s, 3H, OC*H*$_3$), 3.91 (dt, *J* = 4.7, 8.2 Hz, 1H, C*H*OTMP), 4.05 (m, 1H, C*H*OTBS), 4.36 (m, 1H, C*H*OH), 5.24 (dd, *J* = 15.5, 7.9 Hz, 1H, C*H*=CHCHOTMP), 5.45 (dd, *J* = 15.6, 8.0 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –5.2 (q, SiC(*C*$H_3)_2$), –4.9 (q, SiC(*C*$H_3)_2$), 13.7 (q, CH_2*C*H_3), 17.0 (t, NCH_2*C*H_2CH_2CN), 17.6 (s, Si*C*$(CH_3)_3$), 19.9 (q, NC(*C*$H_3)_2$), 20.1 (q, NC(*C*$H_3)_2$), 22.3 (t, *C*H_2CH_3), 24.8 (t, *C*$H_2CH_2CH_2CH_3$), 25.4 (q, SiC(*C*$H_3)_3$), 31.5 (t, *C*$H_2CH_2CH_3$), 33.7 (q, NC(*C*$H_3)_2$), 34.1 (t, TMPOCH*C*H_2), 35.0 (q, NC(*C*$H_3)_2$), 39.8 (t, NC*C*H_2CH_2*C*H_2CN), 42.7 (t, CH*C*H_2CH), 51.4 (d, CH*C*HCH=), 51.5 (q, O*C*H_3), 56.3 (d, *C*HCOOMe), 58.7 (s, N*C*$(CH_3)_2$), 59.7 (s, N*C*$(CH_3)_2$), 74.8 (d, *C*HOH), 78.9 (d, *C*HOTBS), 84.6 (d, *C*HOTMP), 130.7 (d, *C*H=CHCHOTMP), 133.6 (d, =*C*HCHOTMP), 171.9 (s, C=O).

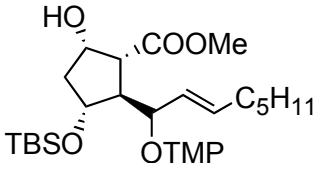
(*1S*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1S* and R*,2E)*-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-2-en-1-yl]cyclopentanecarboxylate 4-52a-CPP3 and 4-52a-CPP4:**



4-52a-CPP3: ^{1}H NMR (400 MHz): δ = –0.01 (s, 6H, Si(C*H*$_3$)$_2$), 0.80 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 0.91-1.02 (m, 12H, NC(C*H*$_3$)$_2$), 1.10-1.46 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.53 (m, 1H, CHC*H*$_2$CH), 1.93 (m, 2H, C*H*$_2$CH=CH), 2.26 (m, 1H, CHC*H*$_2$CH), 2.57 (m, 1H, C*H*CHOTBS), 3.19 (dd, *J* = 8.2, 4.9 Hz, 1H, C*H*COOMe), 3.591 (s, 3H, COOC*H*$_3$), 4.09 (m, 1H, C*H*OTMP), 4.16 (m, 1H, C*H*OTBS), 4.30 (m, 1H, C*H*OH), 5.24 (dd, *J* = 15.3, 9.4 Hz, 1H, =C*H*CHOTMP), 5.35 (m, 1H, CH=C*H*CH$_2$). - ^{13}C NMR (100 MHz): δ = –5.3 (q, Si(*C*H$_3$)$_2$), –5.0 (q, Si(*C*H$_3$)$_2$), 13.6 (q, CH$_2$*C*H$_3$), 16.81 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.27 (s, Si*C*(CH$_3$)$_3$), 19.9 (q, NC(*C*H$_3$)$_2$), 20.16 (q, NC(*C*H$_3$)$_2$), 22.0 (t, *C*H$_2$CH$_3$), 25.3 (q, SiC(*C*H$_3$)$_3$), 27.98 (t, =CHCH$_2$*C*H$_2$), 30.9 (t, *C*H$_2$CH$_2$CH$_3$), 31.9 (t, =CH*C*H$_2$CH$_2$), 33.0 (q, NC(*C*H$_3$)$_2$), 34.3 (q, NC(*C*H$_3$)$_2$), 39.6 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 39.8 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 42.5 (t, CH*C*H$_2$CH), 50.93 (q, COOC*H*$_3$), 53.8 (d, *C*HCOOMe), 54.7 (d, *C*HCHOTBS), 58.3 (s, N*C*(CH$_3$)$_2$), 59.9 (s, N*C*(CH$_3$)$_2$), 74.1 (d, *C*HOTBS), 74.7 (d, *C*HOH), 82.5 (d, *C*HOTMP), 130.1 (d, =*C*HCHOTMP), 134.8 (d, CH=*C*HCH$_2$), 173.0 (s, C=O).

4-52a-CPP4: ^{1}H NMR (400 MHz): δ = –0.03 (s, 3H, Si(C*H*$_3$)$_2$), –0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 0.91-1.02 (m, 12H, NC(C*H*$_3$)$_2$), 1.10-1.46 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.53 (m, 1H, CHC*H*$_2$CH), 1.93 (m, 2H, C*H*$_2$CH=CH), 2.35 (m, 1H, CHC*H*$_2$CH), 2.45 (m, 1H, C*H*CHOTBS), 3.08 (t, *J* = 8.0 Hz, 1H, C*H*COOMe), 3.586 (s, 3H, COOC*H*$_3$), 4.09 (m, 1H, C*H*OTMP), 4.42 (m, 1H, C*H*OTBS), 4.49 (m, 1H, C*H*OH), 5.35 (m, 2H, C*H*=C*H*CH$_2$). - ^{13}C NMR (100 MHz): δ = –5.2 (q, Si(*C*H$_3$)$_2$), –5.0 (q, Si(*C*H$_3$)$_2$), 13.6 (q, CH$_2$*C*H$_3$), 16.77 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.34 (s, Si*C*(CH$_3$)$_3$), 20.24 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.0 (t, *C*H$_2$CH$_3$), 25.3 (q, SiC(*C*H$_3$)$_3$), 28.05 (t, =CHCH$_2$*C*H$_2$), 30.9 (t, *C*H$_2$CH$_2$CH$_3$), 31.8 (t, =CH*C*H$_2$CH$_2$), 33.5 (q, NC(*C*H$_3$)$_2$), 34.0 (q, NC(*C*H$_3$)$_2$), 39.8 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.1 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 42.2 (t, CH*C*H$_2$CH), 50.96 (q, COOC*H*$_3$), 53.3 (d, *C*HCOOMe), 54.7 (d, *C*HCHOTBS), 58.3 (s, N*C*(CH$_3$)$_2$), 59.9 (s, N*C*(CH$_3$)$_2$), 72.6 (d, *C*HOTBS), 73.4 (d, *C*HOH), 82.0 (d, *C*HOTMP), 129.4 (d, =*C*HCHOTMP), 135.1 (d, CH=*C*HCH$_2$), 173.3 (s, C=O).

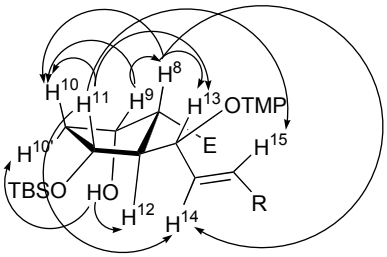
(*1R*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1S* and R*,2E)*-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-2-en-1-yl]cyclopentanecarboxylate 4-52a-CPP1:**



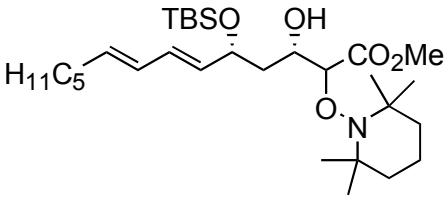
4-52a-CPP1: ^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.79 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 0.85-1.09 (m, 12H, NC(C*H*$_3$)$_2$), 1.12-45 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.65 (m, 1H, CHC*H*$_2$CH), 1.84 (m, 1H, CHC*H*$_2$CH), 1.95 (m, 1H, CH$_2$C*H*$_2$CH=), 2.78 (dd, *J* = 7.4, 4.9 Hz, 1H, C*H*COOMe), 2.86 (t, *J* = 6.6 Hz, 1H, C*H*CHOTBS), 3.41 (d, *J* = 11.2 Hz, 1H, O*H*), 3.64 (s, 3H, COOC*H*$_3$), 3.93 (dd, *J* = 9.4, 6.0 Hz, 1H, C*H*OTMP), 4.25 (br. d, *J* = 4.0 Hz, 1H, C*H*OTBS), 4.35 (m, 1H, C*H*OH), 5.20 (dd, *J* = 15.2, 9.4 Hz, 1H, CH=C*H*CHOTMP), 5.38 (dt, *J* = 15.4, 6.5 Hz, 1H, =C*H*CH$_2$CH$_2$). - ^{13}C NMR (100 MHz): δ = –5.5 (q, Si(*C*H$_3$)$_2$), –5.4 (q, Si(*C*H$_3$)$_2$), 13.3 (q, CH$_2$*C*H$_3$), 16.6 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.0 (s, Si*C*(CH$_3$)$_3$), 19.8 (q, NC(*C*H$_3$)$_2$), 19.9 (q, ONC(*C*H$_3$)$_2$), 21.8 (t, *C*H$_2$CH$_3$), 25.0 (q, SiC(*C*H$_3$)$_3$), 27.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 30.7 (t, *C*H$_2$CH$_2$CH$_3$), 31.9 (t, =CH*C*H$_2$CH$_2$), 33.6 (q, NC(*C*H$_3$)$_2$), 34.2 (q, NC(*C*H$_3$)$_2$), 39.7 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.7 (t, CH*C*H$_2$CH), 50.9 (q, COOC*H*$_3$), 53.25 (d, *C*HCHOTBS or *C*HCOOMe), 53.27 (d, *C*HCHOTBS or *C*HCOOMe), 58.2 (s, N*C*(CH$_3$)$_2$), 60.0 (s, N*C*(CH$_3$)$_2$), 75.9 (d, *C*HOH), 76.6 (d, *C*HOTBS), 84.6 (d, *C*HOTMP), 129.2 (d, CH=*C*HOTMP), 134.8 (d, CH=*C*HCH$_2$), 171.6 (s, C=O).

4-52a-CPP2: ^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.78 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 0.89 (br. s, 3H, NC(C*H*$_3$)$_2$), 0.91 (br. s, 3H, NC(C*H*$_3$)$_2$), 0.97-1.06 (m, 6H, NC(C*H*$_3$)$_2$), 1.12-1.52 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.67 (dt, *J* = 13.7, 4.5 Hz, 1H, CHC*H*$_2^{\beta}$CH), 1.82 (dt, *J* = 12.3, 1.5 Hz, 1H, CHC*H*$_2^{\alpha}$CH), 1.91 (hept, *J* = 7.3 Hz, 2H, C*H*$_2$CH=CH), 2.70 (dd, *J* = 7.7, 5.3 Hz, 1H, C*H*COOMe), 2.86 (dt, *J* = 6.3, 1.4 Hz, 1H, C*H*CHOTBS), 3.41 (d, *J* = 10.5 Hz, 1H, O*H*), 3.62 (s, 3H, COOMe), 3.93 (dd, *J* = 9.4, 6.4 Hz, 1H, C*H*OTMP), 4.23 (m, 1H, C*H*OTBS), 4.31 (dt, *J* = 9.8, 4.9 Hz, 1H, C*H*OH), 5.26 (dd, *J* = 15.2, 9.4 Hz, 1H, CH=C*H*CHOTMP), 5.40 (dt, *J* = 15.3, 6.5 Hz, 1H, CH=C*H*CH$_2$). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.8 (s, Si*C*(CH$_3$)$_3$), 20.6 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.7 (t, =CHCH$_2$*C*H$_2$), 31.5 (t, *C*H$_2$CH$_2$CH$_3$), 32.2 (t, =CH*C*H$_2$CH$_2$), 34.3 (q, NC(*C*H$_3$)$_2$), 35.2 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.3 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 43.0 (t, CH*C*H$_2$CH), 51.7 (q, COOC*H*$_3$),

53.1 (d, *C*HCOOMe), 53.6 (d, *C*HCHOTBS), 58.8 (s, N*C*$(CH_3)_2$), 60.7 (s, N*C*$(CH_3)_2$), 75.7 (d, *C*HOH), 76.0 (d, *C*HOTBS), 84.9 (d, *C*HOTMP), 129.7 (d, CH=*C*HCHOTMP), 135.3 (d, CH=*C*HCH$_2$), 172.7 (s, C=O). - Significant H,H-NOESY interactions:



***(2S or 2R,3S*,5R*,6E,8E)*-Methyl 5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)tetradeca-6,8-dienoate 4-53a:**

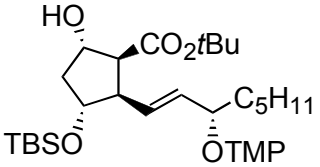


^{1}H NMR (400 MHz): δ = –0.06 (s, 3H, Si(C*H*$_3$)$_2$), –0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.78 (s, 9H, SiC(C*H*$_3$)$_3$), 0.79 (m, 3H, CH$_2$C*H*$_3$), 0.85-1.09 (m, 12H, NC(C*H*$_3$)$_2$), 1.12-1.45 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.60 (m, 1H, OCHC*H*$_2$CHO), 1.71 (m, 1H, OCHC*H*$_2$CHO), 1.95 (m, 2H, CH$_2$C*H*$_2$CH=), 3.63 (s, 3H, OC*H*$_3$), 4.16 (m, 2H, HOC*H*C*H*OTMP), 4.30 (m, 1H, C*H*OTBS), 5.41 (m, 1H, =C*H*CHOTBS), 5.56 (dt, *J* = 14.3, 7.0 Hz, 1H, =C*H*CH$_2$), 5.89 (dd, *J* = 14.8, 10.4 Hz, 1H, CH$_2$CH=C*H*), 6.00 (dd, *J* = 15.0, 10.4 Hz, 1H, C*H*=CHCHOTBS). - ^{13}C NMR (100 MHz): δ = –5.5 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 13.3 (q, CH$_2$*C*H$_3$), 16.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.3 (s, Si*C*(CH$_3$)$_3$), 19.5 (q, NC(*C*H$_3$)$_2$), 19.6 (q, NC(*C*H$_3$)$_2$), 21.8 (t, *C*H$_2$CH$_3$), 25.2 (q, SiC(*C*H$_3$)$_3$), 28.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 30.7 (t, *C*H$_2$CH$_2$CH$_3$), 31.5 (t, =CH*C*H$_2$CH$_2$), 32.3 (q, NC(*C*H$_3$)$_2$), 34.2 (q, ONC(*C*H$_3$)$_2$), 39.5 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 39.6 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 40.5 (t, CH*C*H$_2$CH), 50.7 (q, O*C*H$_3$), 59.2 (s, N*C*$(CH_3)_2$), 59.7 (s, N*C*$(CH_3)_2$), 69.3 (d, *C*HOH), 72.5 (d, *C*HOTBS), 86.6 (d, *C*HOTMP), 128.6 (d, CH$_2$CH=*C*H), 130.0 (d, *C*H=CHCHOTBS), 132.4 (d, =*C*HCHOTBS), 134.7 (d, CH=*C*HCH$_2$), 171.0 (s, C=O).

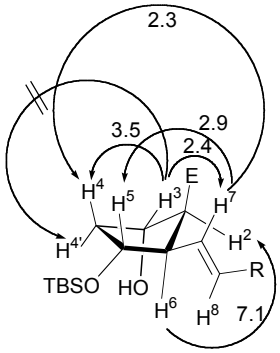
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylates:** IR (Film): $\tilde{\nu}$ = 3515 (w), 2954 (m), 2930 (s), 2858 (w), 1734 (m), 1466 (w), 1366 (m), 1252 (m), 1153 (s), 1129 (m), 1070 (m), 1003 (w), 975 (m), 901 (w), 836 (s), 776 (s), 714 (w), 668 (w). - MS(ESI) *m/z*

(%): 1185 (19) [2M+Na^+], 604 (82) [M+Na^+], 464 (11), 448 (100) [M +Na^+–TEMPO], 158 (12) [$TEMPOH_2$]$^+$. - Combustion analysis: $C_{33}H_{63}NO_5Si$ (581.94): calc. C 68.11, H 10.91, N 2.41; found C 67.93, H 11.01, N 2.36.

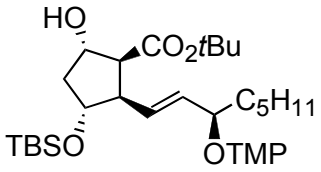
(*1S*,2R*,3R*,5S)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate α-4-8b:**



^{1}H NMR (400 MHz): δ = 0.07 (s, 3H, Si(C*H*$_3$)$_2$), 0.08 (s, 3H, Si(C*H*$_3$)$_2$), 0.88 (m, 3H, CH$_2$C*H*$_3$), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.99-1.15 (m, 12H, NC(C*H*$_3$)$_2$), 1.18-1.34 (m, 7H, NCCH$_2$C*H*$_2$CH$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.35-1.52 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$CHOTMP), 1.42 (s, 9H, OC(C*H*$_3$)$_3$), 1.62 (m, 1H, C*H*$_2$CHOTMP), 1.68 (ddd, *J* = 14.3, 3.2, 1.6 Hz, 1H, CHC*H*$_2$CH), 2.36 (ddd, *J* = 14.3, 7.7, 5.0 Hz, 1H, CHC*H*$_2$CH), 2.50 (d, *J* = 7.2 Hz, 1H, O*H*), 2.97 (br. t, *J* = 8.4 Hz, 1H, C*H*CHOTBS), 3.10 (dd, *J* = 7.8, 5.2 Hz, 1H, C*H*COO*t*Bu), 3.99 (dt, *J* = 7.4, 6.7 Hz, 1H, C*H*OTMP), 4.15 (m, 1H, C*H*OTBS), 4.50 (m, 1H, C*H*OH), 5.18 (dd, *J* = 15.4, 9.0 Hz, 1H, C*H*=CHCHOTMP), 5.53 (ddd, *J* = 15.4, 8.6, 0.6 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H$_3$)$_2$), –4.6 (q, Si(*C*H$_3$)$_2$), 14.1 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.0 (s, Si*C*(CH$_3$)$_3$), 20.3 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.2 (q, OC(*C*H$_3$)$_3$), 32.1 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.9 (t, TMPOCH*C*H$_2$), 35.3 (q, NC(*C*H$_3$)$_2$), 40.3 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.4 (t, CH*C*H$_2$CH), 53.8 (d, *C*HCHOTBS), 57.1 (d, *C*HCOO*t*Bu), 59.0 (s, N*C*(CH$_3$)$_2$), 60.1 (s, N*C*(CH$_3$)$_2$), 74.1 (d, *C*HOH), 78.3 (d, *C*HOTBS), 80.6 (s, O*C*(CH$_3$)$_3$), 84.4 (d, *C*HOTMP), 128.1 (d, *C*H=CHCHOTMP), 136.1 (d, =*C*HCHOTMP), 172.4 (s, C=O). - Significant NOE enhancements:

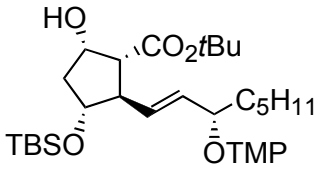


(*1S*,2R*,3R*,5S)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate β-4-8b:**



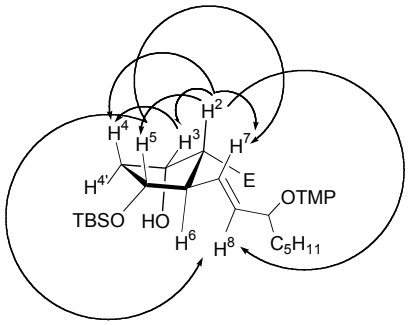
^{1}H NMR (400 MHz): δ = 0.05 (s, 6H, Si(C*H*$_3$)$_2$), 0.87 (m, 3H, CH$_2$C*H*$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.98-1.14 (m, 12H, NC(C*H*$_3$)$_2$), 1.19-1.32 (m, 7H, NCCH$_2$C*H*$_2$CH$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.37-1.51 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$CHOTMP), 1.46 (s, 9H, OC(C*H*$_3$)$_3$), 1.66 (m, 2H, C*H*$_2$CHOTMP, CHC*H*$_2$CH), 2.34 (m, 1H, CHC*H*$_2$CH), 2.52 (m, 1H, O*H*), 2.96 (m, 1H, C*H*CHOTBS), 3.06 (dd, *J* = 8.4, 4.4 Hz, 1H, C*H*COO*t*Bu), 3.99 (m, 1H, C*H*OTMP), 4.10 (dt, *J* = 5.4, 2.7 Hz, 1H, C*H*OTBS), 4.44 (m, 1H, C*H*OH), 5.27 (dd, *J* = 15.6, 8.3 Hz, 1H, C*H*=CHCHOTMP), 5.52 (dd, *J* = 15.5, 6.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.1 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.2 (q, OC(*C*H$_3$)$_3$), 32.0 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.3 (t, TMPOCH*C*H$_2$), 35.3 (q, NC(*C*H$_3$)$_2$), 40.0 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.6 (t, CH*C*H$_2$CH), 53.1 (d, CH*C*HCH=), 56.9 (d, *C*HCOO*t*Bu), 59.0 (s, N*C*(CH$_3$)$_2$), 60.1 (s, N*C*(CH$_3$)$_2$), 74.2 (d, *C*HOH), 78.5 (d, *C*HOTBS), 80.7 (s, O*C*(CH$_3$)$_3$), 84.3 (d, *C*HOTMP), 127.9 (d, *C*H=CHCHOTMP), 135.9 (d, =*C*HCHOTMP), 172.5 (s, C=O).

(*1R*,2R*,3R*,5S)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate α-4-50b:**

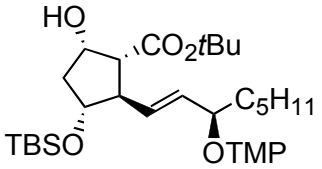


^{1}H NMR (400 MHz): δ = –0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.79 (m, 3H, CH$_2$C*H*$_3$), 0.80 (s, 9H, SiC(C*H*$_3$)$_3$), 0.94-1.10 (m, 12H, NC(C*H*$_3$)$_2$), 1.12-1.20 (m, 7H, NCCH$_2$C*H*$_2$, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.31-1.53 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$CHOTMP), 1.38 (s, 9H, OC(C*H*$_3$)$_3$), 1.59 (m, 1H, C*H*$_2$CHOTMP), 1.78 (br. d, *J* = 13.8 Hz, 1H, CHC*H*$_2$CH), 1.85 (dt, *J* = 13.9, 4.7 Hz, 1H, CHC*H*$_2$CH), 2.52 (dd, *J* = 8.4, 5.3 Hz, 1H, C*H*COO*t*Bu), 3.09 (dt, *J* = 8.1, 5.5 Hz, 1H, C*H*CHOTBS), 3.17 (d, *J* = 9.7 Hz, 1H, O*H*), 3.88 (dt, *J* = 8.4, 4.6 Hz, 1H, C*H*OTMP), 3.94 (m, 1H, C*H*OTBS), 4.32 (m, 1H, C*H*OH), 5.23 (dd, *J* = 15.4, 8.0 Hz, 1H, C*H*=CHCHOTMP), 5.36 (dd, *J* = 15.6, 8.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$),

17.8 (s, Si*C*(CH$_3$)$_3$), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.5 (t, TMPOCH*C*H$_2$), 35.6 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.1 (t, CH*C*H$_2$CH), 51.6 (d, *C*HCHOTBS), 57.2 (d, *C*HCOO*t*Bu), 58.8 (s, N*C*(CH$_3$)$_2$), 60.0 (s, N*C*(CH$_3$)$_2$), 75.3 (d, *C*HOH), 79.6 (d, *C*HOTBS), 80.5 (s, O*C*(CH$_3$)$_3$), 85.0 (d, *C*HOTMP), 131.6 (d, *C*H=CHCHOTMP), 133.8 (d, =*C*HCHOTMP), 170.9 (s, *C*=O). - Significant H,H-NOESY interactions:

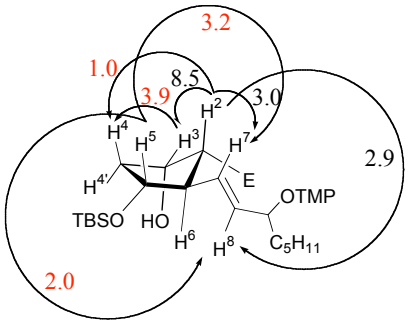


(*1R*,2R*3R*,5S)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarboxylate β-4-50b:**

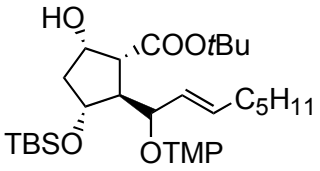


^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H$_3$*)$_2$), 0.02 (s, 3H, Si(C*H$_3$*)$_2$), 0.80 (m, 3H, CH$_2$C*H$_3$*), 0.81 (s, 9H, SiC(C*H$_3$*)$_3$), 0.91-1.09 (m, 12H, NC(C*H$_3$*)$_2$), 1.11-1.25 (m, 7H, NCCH$_2$C*H$_2$*CH$_2$CN, CH$_2$C*H$_2$*C*H$_2$*C*H$_2$*CH$_3$), 1.30-1.54 (m, 6H, NCC*H$_2$*C*H$_2$*C*H$_2$*CN, C*H$_2$*CHOTMP), 1.38 (s, 9H, OC(C*H$_3$*)$_3$), 1.59 (m, 1H, C*H$_2$*CHOTMP), 1.79 (br. d, *J* = 13.8 Hz, 1H, CHC*H$_2$*CH), 1.87 (dt, *J* = 13.8, 4.9 Hz, 1H, CHC*H$_2$*CH), 2.47 (dd, *J* = 8.6, 5.3 Hz, 1H, C*H*COO*t*Bu), 3.10 (m, 1H, C*H*CHOTBS), 3.18 (d, *J* = 9.6 Hz, 1H, O*H*), 3.93 (dt, *J* = 8.3, 4.6 Hz, 1H, C*H*OTMP), 4.02 (m, 1H, C*H*OTBS), 4.33 (m, 1H, C*H*OH), 5.26 (dd, *J* = 15.5, 7.8 Hz, 1H, C*H*=CHCHOTMP), 5.39 (dd, *J* = 15.4, 8.9 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.6 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (s, Si*C*(CH$_3$)$_3$), 17.9 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.2 (q, NC(*C*H$_3$)$_2$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_3$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 31.8 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.4 (t, TMPOCH*C*H$_2$), 35.3 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.1 (t, CH*C*H$_2$CH), 51.4 (d, CH*C*HCH=), 57.4 (d, *C*HCOO*t*Bu), 59.0 (s, N*C*(CH$_3$)$_2$), 60.0 (s, N*C*(CH$_3$)$_2$), 75.1 (d, *C*HOH), 79.1 (d, *C*HOTBS), 80.6 (s, O*C*(CH$_3$)$_3$), 84.9 (d, *C*HOTMP),

131.4 (d, *C*H=CHCHOTMP), 133.6 (d, =*C*HCHOTMP), 170.9 (s, C=O). - Significant NOE enhancements:



(*1R*,2R*,3R*,5S)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1S* and R*,2E)*-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-2-en-1-yl]cyclopentanecarboxylate 4-52b:**



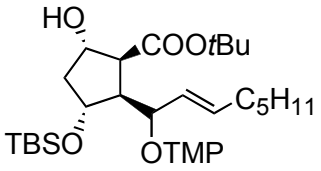
4-52b-CPP1: ^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (s, 9H, SiC(C*H*$_3$)$_3$), 0.81 (m, 3H, CH$_2$C*H*$_3$), 0.92 (br. s, 3H, NC(C*H*$_3$)$_2$), 0.94 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.04 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.07 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.14-1.55 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.39 (s, 9H, OC(C*H*$_3$)$_3$), 1.62 (dt, *J* = 13.5, 4.3 Hz, 1H, CHC*H*$_2$CH), 1.83 (m, 1H, CHC*H*$_2$CH), 1.95 (m, 2H, CH$_2$C*H*$_2$CH=), 2.73 (dd, *J* = 7.4, 4.8 Hz, 1H, C*H*COO*t*Bu), 2.79 (m, 1H, C*H*CHOTBS), 3.32 (d, *J* = 11.3 Hz, 1H, O*H*), 3.91 (dd, *J* = 9.4, 6.2 Hz, 1H, C*H*OTMP), 4.23 (br. d, *J* = 3.8 Hz, 1H, C*H*OTBS), 4.34 (m, 1H, C*H*OH), 5.23 (dd, *J* = 15.3, 9.5 Hz, 1H, CH=C*H*CHOTMP), 5.40 (dt, *J* = 15.2, 6.4 Hz, 1H, =C*H*CH$_2$CH$_2$). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.7 (s, Si*C*(CH$_3$)$_3$), 20.6 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 28.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.5 (t, *C*H$_2$CH$_2$CH$_3$), 32.2 (t, =CH*C*H$_2$CH$_2$), 34.5 (q, NC(*C*H$_3$)$_2$), 34.9 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.4 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 43.3 (t, CH*C*H$_2$CH), 53.8 (d, *C*HCHOTBS or *C*HCOO*t*Bu), 54.8 (d, *C*HCHOTBS or *C*HCOO*t*Bu), 58.9 (s, NC(CH$_3$)$_2$), 60.6 (s, N*C*(CH$_3$)$_2$), 76.9 (d, *C*HOH), 77.4 (d, *C*HOTBS), 80.0 (s, O*C*(CH$_3$)$_3$), 85.3 (d, *C*HOTMP), 130.3 (d, =*C*HCHOTMP), 135.2 (d, CH=*C*HCH$_2$), 171.0 (s, C=O).

The configuration of the ring was assigned by comparison with **4-8b** and **4-50b**. This isomer has very similar chemical shifts to PG isomer **4-50b** but not to IsoP isomer **4-8b**.

4-52b-CPP2: ^{1}H NMR (400 MHz): δ = 0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.05 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (s, 9H, SiC(C*H*$_3$)$_3$), 0.81 (m, 3H, CH$_2$C*H*$_3$), 0.92 (br. s, 3H, NC(C*H*$_3$)$_2$), 0.94 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.04 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.07 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.14-1.55 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.38 (s, 9H, OC(C*H*$_3$)$_3$), 1.62 (dt, *J* = 13.5, 4.3 Hz, 1H, CHC*H*$_2$CH), 1.83 (m, 1H, CHC*H*$_2$CH), 1.95 (m, 2H, CH$_2$C*H*$_2$CH=), 2.64 (dd, *J* = 7.5, 5.3 Hz, 1H, C*H*COO*t*Bu), 2.79 (m, 1H, C*H*CHOTBS), 3.27 (d, *J* = 11.0 Hz, 1H, O*H*), 3.91 (m, 1H, C*H*OTMP), 4.23 (m, 1H, C*H*OTBS), 4.34 (m, 1H, C*H*OH), 5.23 (m, 1H, CH=C*H*CHOTMP), 5.40 (m, 1H, =C*H*CH$_2$CH$_2$). - ^{13}C NMR (100 MHz): δ = –4.7 (q, Si(*C*H$_3$)$_2$), –4.5 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.7 (s, Si*C*(CH$_3$)$_3$), 20.6 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 28.0 (q, OC(*C*H$_3$)$_3$), 28.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 31.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 32.5 (t, =CH*C*H$_2$CH$_2$), 34.5 (q, NC(*C*H$_3$)$_2$), 34.9 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.4 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 42.9 (t, CH*C*H$_2$CH), 52.9 (d, *C*HCHOTBS or *C*HCOO*t*Bu), 54.4 (d, *C*HCHOTBS or *C*HCOO*t*Bu), 60.0 (s, N*C*(CH$_3$)$_2$), 60.6 (s, N*C*(CH$_3$)$_2$), 76.2 (d, *C*HOH), 76.3 (d, *C*HOTBS), 80.0 (s, O*C*(CH$_3$)$_3$), 85.0 (d, *C*HOTMP), 129.9 (d, =*C*HCHOTMP), 134.9 (d, CH=*C*HCH$_2$), 171.0 (s, C=O).

The configuration of the ring was assigned by comparison with **4-8b** and **4-50b**. This isomer has very similar chemical shifts to PG isomer **4-50b** but not to IsoP isomer **4-8b**.

(*1S*,2R*,3R*,5S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*1S* or R*,1E)*-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-2-en-1-yl]cyclopentanecarboxylate 4-52b-CPP3:**



4-52b-CPP3: Detectable resonances: ^{1}H NMR (400 MHz): δ = –0.03 (s, 3H, Si(C*H*$_3$)$_2$), –0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 1.39 (s, 9H, OC(C*H*$_3$)$_3$), 1.96 (m, 2H, C*H*$_2$CH=CH), 2.34 (m, 1H, CHC*H*$_2$CH), 3.01 (t, *J* = 7.9 Hz, 1H, C*H*COO*t*Bu), 4.41 (m, 1H, C*H*OTBS), 4.49 (m, 1H, C*H*OH), 5.51 (dd, *J* = 15.3, 9.2 Hz, 1H, C*H*=CH). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H$_3$)$_2$), –4.5 (q, Si(*C*H$_3$)$_2$), 13.9 (q, CH$_2$*C*H$_3$), 17.8 (s, Si*C*(CH$_3$)$_3$), 20.3 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.2 (q, OC(*C*H$_3$)$_3$), 28.5 (t, =CHCH$_2$*C*H$_2$), 31.3 (t, *C*H$_2$CH$_2$CH$_3$), 32.2 (t, =CH*C*H$_2$CH$_2$), 32.5 (q, NC(*C*H$_3$)$_2$), 33.9 (q, NC(*C*H$_3$)$_2$), 40.1 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.2 (t, CH*C*H$_2$CH), 55.0 (d, *C*HCOO*t*Bu), 55.3 (d, *C*HCHOTBS), 58.7 (s, N*C*(CH$_3$)$_2$), 60.4 (s, N*C*(CH$_3$)$_2$), 72.3 (d, *C*HOTBS), 73.9 (d, *C*HOH),

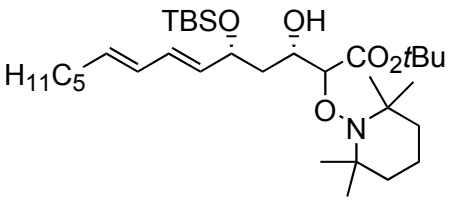
80.1 (s, O*C*$(CH_3)_3$), 82.1 (d, *C*HOTMP), 130.5 (d, =*C*HCHOTMP), 134.2 (d, CH=*C*HCH_2), 172.8 (s, C=O).

Detectable resonances of an unknown cyclic product: ^{1}H NMR (400 MHz): δ = 2.92 (m, 1H), 3.02 (m, 1H), 4.21 (m, 1H).

Table 6.5: Significant NMR data of compounds 15α,β-**4-8a,b** and 15α,β-**4-50a,b**

^{1}H NMR	H8	H9	H11	H12	H13	H14	H15
15α-**4-8a**	3.18 (dd)	4.52 (m)	4.08 (m)	2.96 (m)	5.01 (dd)	5.43 (dd)	3.87 (dt)
15β-**4-8a**	3.15 (dd)	4.47 (m)	4.01 (dt)	2.96 (m)	5.10 (dd)	5.42 (dd)	3.92 (dt)
15α-**4-8b**	3.10 (dd)	4.50 (m)	4.15 (m)	2.97 (t)	5.18 (dd)	5.53 (dd)	3.99 (dt)
15β-**4-8b**	3.06 (dd)	4.44 (m)	4.10 (dt)	2.96 (m)	5.27 (dd)	5.52 (dd)	3.99 (m)
15α-**4-50a**	2.65 (dd)	4.39 (m)	4.01 (dt)	3.18 (m)	5.22 (dd)	5.38 (dd)	3.89 (m)
15β-**4-50a**	2.59 (dd)	4.33 (m)	4.02 (m)	3.10 (m)	5.26 (dd)	5.39 (dd)	3.93 (dt)
15α-**4-50b**	2.52 (dd)	4.32 (m)	3.94 (m)	3.09 (t)	5.23 (dd)	5.36 (ddd)	3.88 (dt)
15β-**4-50b**	2.47 (dd)	4.33 (m)	4.02 (dt)	3.10 (m)	5.26 (dd)	5.39 (dd)	3.93 (m)
^{13}C NMR	C8	C9	C11	C12	C13	C14	C15
15α-**4-8a**	56.6 (d)	74.1 (d)	78.4 (d)	54.4 (d)	127.5 (d)	136.9 (d)	84.7 (d)
15β-**4-8a**	56.1 (d)	74.1 (d)	78.6 (d)	53.6 (d)	127.7 (d)	136.1 (d)	84.5 (d)
15α-**4-8b**	57.1 (d)	74.1 (d)	78.3 (d)	53.8 (d)	128.1 (d)	136.1 (d)	84.4 (d)
15β-**4-8b**	56.9 (d)	74.2 (d)	78.5 (d)	53.1 (d)	127.9 (d)	135.9 (d)	84.3 (d)
15α-**4-50a**	56.6 (d)	75.2 (d)	79.5 (d)	51.9 (d)	131.2 (d)	134.3 (d)	84.9 (d)
15β-**4-50a**	56.3 (d)	74.8 (d)	78.9 (d)	51.4 (d)	130.7 (d)	133.6 (d)	84.6 (d)
15α-**4-50b**	57.2 (d)	75.3 (d)	79.6 (d)	51.6 (d)	131.6 (d)	133.8 (d)	85.0 (d)
15β-**4-50b**	57.4 (d)	75.1 (d)	79.1 (d)	51.4 (d)	131.4 (d)	133.6 (d)	84.9 (d)

(*2S* or 2R,3*S**,5*R**,6*E*,8*E*)-*tert*-Butyl 5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-6,8-tetradecadienoate 4-53b:**



^{1}H NMR (400 MHz): δ = –0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.82 (s, 9H, SiC(C*H*$_3$)$_3$), 0.83 (m, 3H, CH_2C*H*$_3$), 0.94-1.14 (m, 12H, NC(C*H*$_3$)$_2$), 1.16-1.53 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH_2C*H*$_2$C*H*$_2$C*H*$_2$$CH_3$), 1.42 (s, 9H, OC(C*H*$_3$)$_3$), 1.53-1.67 (m, 2H,

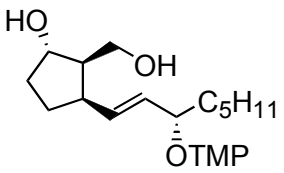
OCHCH_2CHO), 1.99 (m, 2H, CH_2CH=), 4.06 (m, 1H, C*H*OTMP), 4.14 (m, 1H, C*H*OH), 4.31 (m, 1H, C*H*OTBS), 5.43 (m, 1H, =C*H*CHOTBS), 5.58 (dt, *J* = 14.4, 7.0 Hz, 1H, =C*H*CH_2), 5.92 (dd, *J* = 14.9, 10.4 Hz, 1H, CH_2CH=C*H*), 6.04 (dd, *J* = 15.0, 10.4 Hz, 1H, C*H*=CHCHOTBS). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H_3)$_2$), –4.1 (q, Si(*C*H_3)$_2$), 14.0 (q, CH_2*C*H_3), 17.1 (t, NCCH_2*C*H_2CH_2CN), 18.1 (s, Si*C*$(CH_3)_3$), 20.1 (q, NC(*C*H_3)$_2$), 20.6 (q, NC(*C*H_3)$_2$), 22.5 (t, *C*H_2CH$_3$), 25.9 (q, SiC(*C*H_3)$_3$), 28.1 (q, OC(*C*H_3)$_3$), 28.9 (t, *C*H_2CH_2CH_2CH$_3$), 31.4 (t, *C*H_2CH_2CH$_3$), 32.6 (t, =CH*C*H_2), 34.5 (q, NC(*C*H_3)$_2$), 39.6 (t, NC*C*H_2CH_2*C*H_2CN), 40.4 (t, CH*C*H_2CH), 60.3 (s, N*C*$(CH_3)_2$), 69.8 (d, *C*HOH), 72.3 (d, *C*HOTBS), 81.5 (s, O*C*$(CH_3)_3$), 87.7 (d, *C*HOTMP), 129.4 (d, CH_2CH=*C*H), 130.8 (d, *C*H=CHCHOTBS), 133.2 (d, =*C*HCHOTBS), 135.1 (d, CH=*C*HCH_2), 170.2 (s, C=O).

6.9.3. Reduction of cyclopentanecarboxylic esters 15α,β-4-7b and 15α,β-4-8a,b

Reduction of cyclopentanecarboxylic esters 15α-4-7b and 15β-4-7b:
To a suspension of fresh $LiAlH_4$ (68 mg, 1.8 mmol) in 3 mL THF was added **4-7b** (80 mg, 0.18 mmol) dissolved in 3 mL THF slowly at –40 °C with good stirring. The solution was warmed to 0 °C during 2.5 h and stirred at r.t. for 0.5 h. The reaction was quenched with 15 drops of water at 0 °C, and stirred for further 15 min. The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel, which was washed thoroughly with diethyl ether. After evaporation of the solvent, the product was purified by flash chromatography (hexane/ethyl acetate 2:1) to give 70 mg (100%) of the pure diol **4-54** as a mixture of inseparable 15α- and 15β-diastereomers as a colourless oil, R_f(hexane/ethyl acetate 2:1) = 0.14. Similar reductions were performed on PG isomers 15α-**4-45b** and 15β-**4-45b**. The configuration of the diols was assigned by analogy to the substrates used.

2-Hydroxymethyl-3-[(*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ols: MS(ESI) *m/z* (%): 404 (100) [M+Na^+], 248 (39) [M–TEMPO+Na^+], 158 (8) [$TEMPOH_2$]$^+$. - HRMS: $C_{23}H_{43}NO_3Na^+$: calc. 404.3141; found 404.3150.

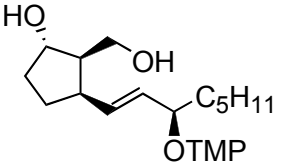
(*1S*,2R*,3R)-2-Hydroxymethyl-3-[(*E,S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15α-4-54:**



^{1}H NMR (400 MHz): δ = 0.88 (t, *J* = 6.8 Hz, 3H, CH_2C*H*$_3$), 1.05 (br. s, 6H, NC(C*H*$_3$)$_2$), 1.12 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.16 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.19-1.42 (m, 12H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN,

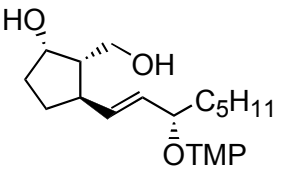
$CH_2CH_2CH_2CH_2CH_3$, $CH_2CHOTMP$), 1.50-1.70 (m, 4H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$, CH_2CH_2CHOH), 1.91 (m, 1H, CH_2CH_2CHOH), 2.15 (m, 2H, CH_2CHOH, $CHCH_2OH$), 2.79 (br. s, 1H, OH), 2.87 (m, 1H, $CHCH{=}CHCHOTMP$), 3.01 (br. s, 1H, OH), 3.59 (A part of ABX system, J = 16.8, 6.7 Hz, 1H, CH_2OH), 3.68 (B part of ABX system, J = 16.8, 6.3 Hz, 1H, CH_2OH), 4.09 (m, 1H, $CHOTMP$), 4.16 (m, 1H, $CHOH$), 5.38 (ddd, J = 15.5, 9.0, 1.3 Hz, 1H, $=CHCHOTMP$), 5.60 (dd, J = 15.5, 7.0 Hz, $CH{=}CHCHOTMP$). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.2 (t, $NCCH_2CH_2CH_2CN$), 20.5 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.2 (t, $CH_2CH_2CH_3CH_3$), 27.5 (t, CH_2CH_2CHOH), 31.9 (t, $CH_2CH_2CH_3$), 33.5 (t, CH_2CHOH), 34.0 (q, $NC(CH_3)_2$), 34.5 (t, $CH_2CHOTMP$), 34.8 (q, $NC(CH_3)_2$), 39.6 (t, $NCCH_2CH_2CH_2CN$), 39.8 (t, $NCCH_2CH_2CH_2CN$), 41.8 (d, $CHCHCH{=}$), 53.2 (d, $CHCH_2OH$), 59.1 (s, $NC(CH_3)_2$), 60.5 (s, $NC(CH_3)_2$), 62.7 (t, CH_2OH), 76.4 (d, $CHOH$), 84.6 (d, $CHOTMP$), 132.4 (d, $=CHCHOTMP$), 133.5 (d, $CH{=}CHCHOTMP$).

(*1S*,2R*,3R)-2-Hydroxymethyl-3-[(*E,R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15β-4-54:**



Detectable resonances: ^1H NMR (400 MHz): δ = 2.15 (m, 2H, CH_2CHOH, $CHCH_2OH$), 2.82 (br. s, 2H, OH), 2.87 (m, 1H, $CHCH{=}CHCHOTMP$), 3.76 (m, 2H, CH_2OH), 4.16 (m, 2H, $CHOH$, $CHOTMP$), 5.43 (m, 1H, $=CHCHOTMP$), 5.49 (dd, J = 14.9, 8.8 Hz, 1H, $CH{=}CHCHOTMP$). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.2 (t, $NCCH_2CH_2CH_2CN$), 20.5 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.2 (t, $CH_2CH_2CH_3CH_3$), 29.0 (t, CH_2CH_2CHOH), 31.9 (t, $CH_2CH_2CH_3$), 33.3 (t, CH_2CHOH), 34.0 (q, $NC(CH_3)_2$), 34.5 (t, $CH_2CHOTMP$), 34.8 (q, $NC(CH_3)_2$), 39.6 (t, $NCCH_2CH_2CH_2CN$), 42.7 (d, $CHCHCH{=}$), 54.0 (d, $CHCH_2OH$), 61.5 (t, CH_2OH), 74.7 (d, $CHOH$), 84.1 (d, $CHOTMP$), 133.0 (d, $=CHCHOTMP$), 135.6 (d, $CH{=}CHCHOTMP$).

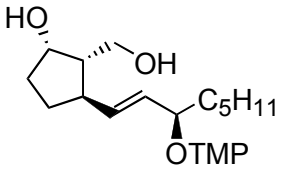
(*1S*,2S*,3R)-2-Hydroxymethyl-3-[(*E,S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15α-4-55:**



^1H NMR (200 MHz): δ = 0.88 (t, J = 6.5 Hz, 3H, CH_2CH_3), 1.05-1.47 (m, 27H, $NC(CH_3)_2$, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$, OH), 1.70 (m, 3H, CH_2CH_2CHOH), 2.03 (m, 2H,

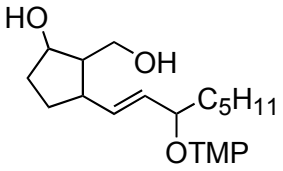
C*H*$_2$CHOH, C*H*CH$_2$OH), 2.17 (br. s, 1H, OH), 2.61 (m, 1H, C*H*CH=CHCHOTMP), 3.86 (AB part of ABX system, *J* = 11.0, 11.2, 5.3 Hz, 2H, C*H*$_2$OH), 4.07 (m, 1H, C*H*OTMP), 4.42 (dt, *J* = 2.7, 5.5 Hz, 1H, C*H*OH), 5.34 (dd, *J* = 15.3, 8.1 Hz, 1H, =C*H*CHOTMP), 5.48 (dd, *J* = 15.3, 8.2 Hz, C*H*=CHCHOTMP). - ^{13}C NMR (50 MHz): δ = 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.2 (t, *C*H$_2$CH$_2$CH$_3$CH$_3$), 30.4 (t, *C*H$_2$CH$_2$CHOH), 31.8 (t, *C*H$_2$CH$_2$CH$_3$), 34.4 (q, NC(*C*H$_3$)$_2$), 34.6 (t, *C*H$_2$CHOH), 35.0 (q, NC(*C*H$_3$)$_2$), 34.7 (t, *C*H$_2$CHOTMP), 39.9 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 43.4 (d, *C*HCH=CHCHOTMP), 52.8 (d, *C*HCH$_2$OH), 60.0 (q, N*C*(CH$_3$)$_2$), 62.2 (t, *C*H$_2$OH), 75.4 (d, *C*HOH), 84.6 (d, *C*HOTMP), 133.1 (d, =*C*H), 135.5 (d, *C*H=).

(*1S*,2S*,3R)-2-Hydroxymethyl-3-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15β-4-55:**



Detectable resonances: ^{1}H NMR (200 MHz): δ = 2.03 (m, 2H, C*H*$_2$CHOH, C*H*CH$_2$OH), 2.61 (m, 1H, C*H*CH=CHCHOTMP), 3.86 (m, 2H, C*H*$_2$OH), 4.07 (m, 1H, C*H*OTMP), 4.42 (m, 1H, C*H*OH), 5.34 (m, 2H, C*H*=C*H*). - ^{13}C NMR (50 MHz): δ = 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.3 (t, *C*H$_2$CH$_2$CH$_3$CH$_3$), 30.0 (t, *C*H$_2$CH$_2$CHOH), 31.8 (t, *C*H$_2$CH$_2$CH$_3$), 34.4 (t, *C*H$_2$CHOH), 34.7 (t, *C*H$_2$CHOTMP), 39.9 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 42.0 (d, CH*C*HCH=), 51.6 (d, *C*HCH$_2$OH), 61.5 (t, *C*H$_2$OH), 75.3 (d, *C*HOH), 85.1 (d, *C*HOTMP), 133.3 (d, =*C*H), 134.5 (d, *C*H=).

2-Hydroxymethyl-3-[(*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 4-56:



4-56-I$_{3\text{-}2}$ (detectable resonances): ^{1}H NMR (400 MHz): δ = 2.87 (m, 1H, C*H*CH=CHCHOTMP), 3.31 (br. s, 1H, OH), 3.53 (dd, *J* = 10.4, 8.7 Hz, 1H, C*H*$_2$OH), 3.62 (dd, *J* = 10.5, 4.4 Hz, 1H, C*H*$_2$OH or C*H*OH), 3.98 (dt, *J* = 4.8, 8.4 Hz, 1H, C*H*OTMP), 5.31 (dd, *J* = 15.4, 8.3 Hz, =C*H*CHOTMP), 5.38 (m, 1H, C*H*=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 29.3 (t, *C*H$_2$CH$_2$CHOH), 33.0 (t, *C*H$_2$CHOH), 34.4 (t, *C*H$_2$CHOTMP), 40.2 (t,

NC*C*H_2CH_2CH_2CN), 43.5 (d, CH*C*HCH=), 55.1 (d, *C*HCH_2OH), 64.7 (t, *C*H_2OH), 77.5 (d, *C*HOH), 84.9 (d, *C*HOTMP), 133.1 (d, =*C*HCHOTMP), 134.6 (d, *C*H=CHCHOTMP).

Reduction of cyclopentanecarboxylic esters 4-8a,b:

4-57 from 4-8a (Method A): To a suspension of fresh $LiAlH_4$ (40 mg, 1.05 mmol) in 3 mL THF was added **4-8a** (60 mg, 0.11 mmol) dissolved in 2 mL THF slowly at –45 °C with good stirring. The solution was warmed to r.t. during 1 h and stirred for another hour. The reaction was quenched with 10 drops of water at 0 °C, diluted with diethyl ether and stirred for 20 min at room temperature. The reaction mixture was filtered through a pad of silica gel, which was washed thoroughly with diethyl ether. After evaporation of the solvent, the product was purified by flash chromatography (hexane/ethyl acetate 2:1) to give 50 mg (89%) of the pure diol **4-57** as a mixture of inseparable 15α- and 15β-diastereomers as a colourless oil, R_f(hexane/ethyl acetate 2:1) = 0.38. Reductions were similarly performed with mixtures of α-**4-8a**, β-**4-8a** and α-**4-50a**. The inseparable diastereomers of α- and β-**4-57** and the diol with PG configuration **4-58** were further enriched by another flash chromatography.

4-57 from 4-8b (Method B): To a suspension of $LiAlH_4$ (55 mg, 1.44 mmol) in 5 mL THF was added **4-8b** (280 mg, 0.48 mmol) dissolved in 2 mL THF slowly at –70 °C with good stirring. The solution was warmed to 0 °C during 1.5 h, and stirred at 0 °C for 30 min. The reaction mixture was quenched carefully with 10 drops of water at 0 °C, diluted with diethyl ether and stirred at r.t. for 20 min. The reaction mixture was filtered through a pad of silicagel, which was washed thoroughly with diethyl ether. After evaporation of the solvent, flash chromatography (hexane/ethyl acetate 10:1, gradient to 2:1) gave 40 mg (16%) of the aldehyde **4-59** as a colourless oil, R_f(hexane/ethyl acetate 2:1) = 0.9; 130 mg (53%) of pure diol **4-57** as colourless oil and at last 20 mg (8%) of the TBS-deprotected cyclopentane ester **4-60**, R_f(hexane/ethyl acetate 2:1) = baseline.

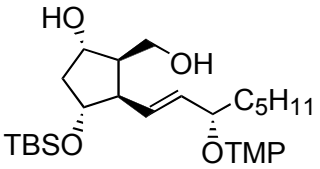
Variations of workup:

Method C: The reaction was quenched with 1 mL ethyl acetate at –70 °C. After 5 min 0.3 mL of water was added, and after another 5 min the mixture was diluted with diethyl ether and allowed to warm to r.t. Then 3 g of silica gel was added and it was stirred for 30 min. This mixture was then filtered using a frit.

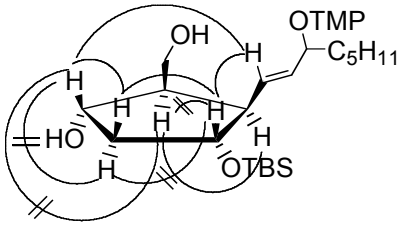
Method D: The reaction was quenched with 20 mL of solution of sodium potassium tartrate at 0 °C, diluted with diethyl ether and warmed to r.t., followed by a standard aqueous workup.

4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethyl-3-[(*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ols: IR (Film): $\tilde{\nu}$ = 3381 (w), 2928 (s), 2857 (m), 1465 (m), 1376 (w), 1360 (w), 1254 (m), 1182 (w), 1130 (m), 1098 (m), 1061 (m), 1025 (m), 976 (m), 836 (s), 775 (s), 715 (w). - MS(ESI) *m/z* (%): 512 (100) [M+H$^+$], 158 (13) [TEMPOH$_2$]$^+$. - HRMS: $C_{29}H_{58}NO_4Si$: calc. 512.4135; found 512.4130.

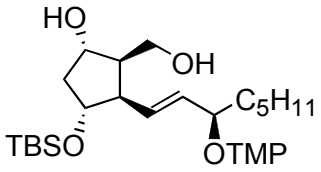
(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethyl-3-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15α-4-57:**



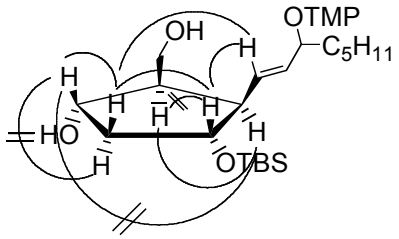
^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.82 (m+s, 12H, CH$_2$C*H*$_3$ + SiC(C*H*$_3$)$_3$), 0.99 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.00 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.05 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.08 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.13-1.28 (m, 8H, NCCH$_2$C*H*$_2$CH$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.30-1.53 (m, 5H, NCC*H*$_2$CH$_2$C*H*$_2$CN, TMPOCHC*H*$_2$), 1.59 (m, 1H, TMPOCHC*H*$_2$), 1.64 (dt, *J* = 13.8, 4.3 Hz, 1H, CHC*H*$_2$CH), 2.20 (br. s, 2H, OH), 2.25 (ddd, *J* = 13.7, 7.1, 5.3 Hz, 1H, CHC*H*$_2$CH), 2.36 (m, 1H, C*H*CH$_2$OH), 2.75 (dt, *J* = 8.4, 3.4 Hz, 1H, TBSOCHC*H*), 3.61 (AB part of ABX system, *J* = 11.4, 6.5, 6.0 Hz, 2H, C*H*$_2$OH), 4.00 (dt, *J* = 5.3, 8.2 Hz, 1H, C*H*OTMP), 4.08 (m, 2H, C*H*OH, C*H*OTBS), 5.27 (dd, *J* = 15.5, 8.4 Hz, 1H, C*H*=CHCHOTMP), 5.44 (ddd, *J* = 15.5, 8.8, 0.9 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.7 (q, Si(*C*H$_3$)$_2$), –4.6 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.5 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.2 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 34.1 (q, NC(*C*H$_3$)$_2$), 34.6 (t, TMPOCH*C*H$_2$), 35.0 (q, NC(*C*H$_3$)$_2$), 40.1 (t, NC*C*H$_2$CH$_2$C*H*$_2$CN), 43.3 (t, CH*C*H$_2$CH), 52.2 (d, CH*C*HCH=), 52.6 (d, *C*HCH$_2$OH), 59.2 (s, N*C*(CH$_3$)$_2$), 62.9 (t, *C*H$_2$OH), 75.5 (d, *C*HOH), 76.7 (d, *C*HOTBS), 84.8 (d, *C*HOTMP), 129.8 (d, *C*H=CHCHOTMP), 134.7 (d, =*C*HCHOTMP). - H,H-NOESY of 15α-**4-57**:



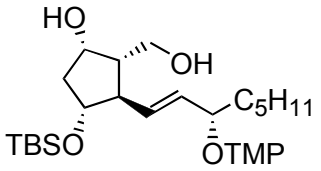
(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethyl-3-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15β-4-57:**



^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.83 (m+s, 12H, SiC(C*H*$_3$)$_3$ + CH$_2$C*H*$_3$), 1.01 (s, 3H, NC(C*H*$_3$)$_2$), 1.04 (s, 3H, NC(C*H*$_3$)$_2$), 1.09 (s, 3H, NC(C*H*$_3$)$_2$), 1.10 (s, 3H, NC(C*H*$_3$)$_2$), 1.14-1.63 (m, 14H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.68 (dt, *J* = 13.8, 3.5 Hz, 1H, CHC*H*$_2$CH), 2.16 (ddd, *J* = 13.7, 6.9, 5.0 Hz, 1H, CHC*H*$_2$CH), 2.44 (m, 2H, C*H*CH$_2$O*H*), 2.76 (m, 1H, TBSOCHC*H*), 3.08 (br. s, 1H, O*H*), 3.69 (A part of ABX system, *J* = 11.9, 7.9 Hz, 1H, C*H*$_2$OH), 3.76 (B part of ABX system, *J* = 11.8, 4.6 Hz, 1H, C*H*$_2$OH), 3.89 (m, 1H, C*H*OTBS), 4.00 (m, 1H, C*H*OH), 4.11 (m, 1H, C*H*OTMP), 5.28 (dd, *J* = 15.4, 10.7 Hz, 1H, C*H*=CHCHOTMP), 5.51 (dd, *J* = 15.1, 9.4 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.8 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.0 (s, Si*C*(CH$_3$)$_3$), 20.6 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.2 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 34.2 (q, NC(*C*H$_3$)$_2$), 34.5 (t, TMPOCH*C*H$_2$), 39.1 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 39.6 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 43.0 (t, CH*C*H$_2$CH), 53.4 (d, CH*C*HCH=), 53.6 (d, *C*HCH$_2$OH), 59.4 (s, N*C*(CH$_3$)$_2$), 60.9 (s, N*C*(CH$_3$)$_2$), 61.4 (t, *C*H$_2$OH), 74.3 (d, *C*HOH), 78.3 (d, *C*HOTBS), 84.0 (d, *C*HOTMP), 132.5 (d, *C*H=CHCHOTMP), 135.3 (d, =*C*HCHOTMP). - H,H-NOESY of 15β-**17**:



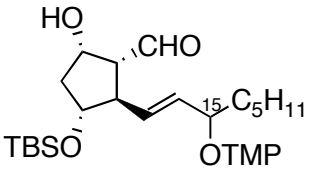
(*1S*,2S*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethyl-3-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 4-58:**



^{1}H NMR (400 MHz): δ = –0.01 (s, 6H, Si(C*H*$_3$)$_2$), 0.82 (s+m, 12H, SiC(C*H*$_3$)$_3$ + CH$_2$C*H*$_3$), 0.99 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.01 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.05 (br. s, 3H, NC(C*H*$_3$)$_2$), 1.08 (br.

s, 3H, NC(C*H*$_3$)$_2$), 1.14-1.24 (m, 7H, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, NCCH$_2$C*H*$_2$CH$_2$CN), 1.30-1.52 (m, 6H, NCC*H*$_2$C*H*$_2$C*H*$_2$CCN, TMPOCHC*H*$_2$), 1.60 (m, 1H, TMPOCHC*H*$_2$), 1.73 (br. d, *J* = 14.2 Hz, 1H, CHC*H*$_2$CH), 1.82 (m, 1H, C*H*CH$_2$OH), 1.99 (dt, *J* = 14.0, 5.4 Hz, 1H, CHC*H*$_2$CH), 2.45 (dt, *J* =3.5, 8.8 Hz, 1H, TBSOCHC*H*), 2.82 (br. s, 1H, O*H*), 3.00 (br. d, *J* = 8.2 Hz, 1H, O*H*), 3.80 (m, 2H, C*H*$_2$OH), 3.95 (m, 1H, C*H*OTBS), 3.99 (m, 1H, C*H*OTMP), 4.28 (m, 1H, C*H*OH), 5.23 (dd, *J* = 15.3, 8.9 Hz, 1H, C*H*=CHCHOTMP), 5.41 (dd, *J* = 15.4, 9.1 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.8 (s, Si*C*(CH$_3$)$_3$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.6 (t, TMPOCH*C*H$_2$), 35.2 (q, NC(*C*H$_3$)$_2$), 39.7 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.0 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 43.4 (t, CH*C*H$_2$CH), 52.0 (d, *C*HCH$_2$OH), 52.9 (d, CH*C*HCH=), 59.0 (s, N*C*(CH$_3$)$_2$), 59.1 (s, N*C*(CH$_3$)$_2$), 62.4 (t, *C*H$_2$OH), 75.0 (d, *C*HOH), 79.3 (d, *C*HOTBS), 84.7 (d, *C*HOTMP), 132.8 (d, *C*H=CHCHOTMP), 134.2 (d, =*C*HCHOTMP). - MS(ESI) *m/z* (%): 1045 (18) [2M+Na$^+$], 534 (84) [M+Na$^+$], 378 (100) [M+Na$^+$–TEMPO], 158 (8) [TEMPOH$_2$]$^+$. - HRMS: C$_{29}$H$_{58}$NO$_4$Si: calc. 512.4135; found M+H$^+$ 512.4133.

(*1R*,2R*,3R*,5S)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-[(*R* and S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanecarbaldehyde 4-59:**

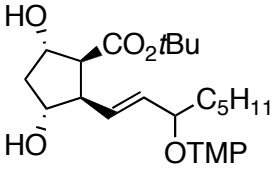


15α-**4-59**: R$_f$(hexane/ethyl acetate 2:1) = 0.9. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.812 (s, 9H, SiC(C*H*$_3$)$_3$), 0.83 (m, 3H, CH$_2$C*H*$_3$), 1.00-1.09 (m, 12H, NC(C*H*$_3$)$_2$), 1.14-1.57 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$CHOTMP), 1.69 (m, 1H, C*H*$_2$CHOTMP), 1.90 (m, 2H, CHC*H*$_2$CH), 2.48 (m, 1H, C*H*CHO), 2.66 (m, 1H, C*H*CHOTBS), 4.02 (m, 1H, C*H*OTMP), 4.58 (m, 1H, C*H*OTBS), 4.63 (m, 1H, C*H*OH), 5.48 (m, 2H, C*H*=C*H*CHOTMP), 9.65 (d, *J* = 1.2 Hz, 1H, C*H*O). - ^{13}C NMR (100 MHz): δ = –4.5 (q, Si(*C*H$_3$)$_2$), –4.4 (q, Si(*C*H$_3$)$_2$), 14.3 (q, CH$_2$*C*H$_3$), 17.5 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.2 (s, Si*C*(CH$_3$)$_3$), 20.5 (q, NC(*C*H$_3$)$_2$), 20.6 (q, NC(*C*H$_3$)$_2$), 22.8 (t, *C*H$_2$CH$_3$), 25.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.99 (q, SiC(*C*H$_3$)$_3$), 32.1 (t, *C*H$_2$CH$_2$CH$_3$), 34.2 (q, NC(*C*H$_3$)$_2$), 34.7 (t, TMPOCH*C*H$_2$), 35.4 (q, NC(*C*H$_3$)$_2$), 40.4 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.7 (t, CH*C*H$_2$CH), 51.9 (d, CH*C*HCH=), 59.4 (s, N*C*(CH$_3$)$_2$), 60.3 (s, N*C*(CH$_3$)$_2$), 64.2 (d, *C*HCHO), 71.1 (d, *C*HOH),

77.0 (d, *C*HOTBS), 84.8 (d, *C*HOTMP), 130.8 (d, *C*H=CHCHOTMP), 135.1 (d, =*C*HCHOTMP), 202.3 (d, CHO).

15β-**4-59**: ^{1}H NMR (400 MHz): δ = –0.02 (s, 6H, Si(C*H*$_3$)$_2$), 0.808 (s, 9H, SiC(C*H*$_3$)$_3$), 0.83 (m, 3H, CH$_2$C*H*$_3$), 1.00-1.09 (m, 12H, NC(C*H*$_3$)$_2$), 1.14-1.57 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$CHOTMP), 1.69 (m, 1H, C*H*$_2$CHOTMP), 1.90 (m, 2H, CHC*H*$_2$CH), 2.48 (m, 1H, C*H*CHO), 2.66 (m, 1H, C*H*CHOTBS), 4.02 (m, 1H, C*H*OTMP), 4.58 (m, 1H, C*H*OTBS), 4.61 (m, 1H, C*H*OH), 5.44 (m, 2H, C*H*=C*H*CHOTMP), 9.69 (d, *J* = 0.9 Hz, 1H, C*H*O). - ^{13}C NMR (100 MHz): δ = –4.5 (q, Si(*C*H$_3$)$_2$), –4.4 (q, Si(*C*H$_3$)$_2$), 14.3 (q, CH$_2$*C*H$_3$), 17.4 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.3 (s, Si*C*(CH$_3$)$_3$), 20.5 (q, NC(*C*H$_3$)$_2$), 20.6 (q, NC(*C*H$_3$)$_2$), 22.8 (t, *C*H$_2$CH$_3$), 25.3 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.96 (q, SiC(*C*H$_3$)$_3$), 32.2 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (t, TMPOCH*C*H$_2$), 34.2 (q, NC(*C*H$_3$)$_2$), 35.4 (q, NC(*C*H$_3$)$_2$), 40.3 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.1 (t, CH*C*H$_2$CH), 52.1 (d, CH*C*HCH=), 59.4 (s, N*C*(CH$_3$)$_2$), 60.3 (s, N*C*(CH$_3$)$_2$), 64.1 (d, *C*HCHO), 70.7 (d, *C*HOH), 76.9 (d, *C*HOTBS), 84.9 (d, *C*HOTMP), 131.1 (d, *C*H=CHCHOTMP), 135.7 (d, =*C*HCHOTMP), 202.3 (d, CHO).

(*1S*,2R*,3R*,5S)-*tert*-Butyl 3,5-dihydroxy-2-[(*R* and S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate 4-60:**



R$_f$(hexane/ethyl acetate 2:1) = baseline. - IR (Film): $\tilde{\nu}$ = 3407 (br. w), 2931 (s), 2859 (w), 1723 (m), 1367 (m), 1256 (w), 1153 (m), 1077 (w), 974 (w) cm^{-1}. - MS(ESI) *m/z* (%): 490 (10) [M+Na$^+$], 468 (100) [M+H$^+$], 334 (12) [M+Na$^+$–TEMPO], 158 (26) [TEMPOH$_2^+$]. - HRMS: C$_{27}$H$_{50}$NO$_5^+$: calc. 468.3689; found 468.3683.

15α-**4-60**: ^{1}H NMR (400 MHz): δ = 0.84 (m, 3H, CH$_2$C*H*$_3$), 1.01-1.07 (m, 12H, NC(C*H*$_3$)$_2$), 1.15-1.55 (m, 14H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$CHOTMP, OH), 1.39 (s, 9H, OC(C*H*$_3$)$_3$), 1.49 (br. s, 1H, OH), 1.61 (m, 2H, C*H*$_2$CHOTMP, CHC*H*$_2$CH), 2.49 (ddd, *J* = 17.7, 13.8, 7.1 Hz, 1H, CHC*H*$_2$CH), 2.86 (m, 1H, OHCHC*H*CH=), 2.95 (dd, *J* = 8.6, 4.6 Hz, 1H, C*H*COO*t*Bu), 4.00 (m, 1H, C*H*OTMP), 4.08 (m, 1H, HOC*H*CHCH=), 4.49 (m, 1H, C*H*(OH)CHCOO*t*Bu), 5.24 (dd, *J* = 15.3, 9.0 Hz, 1H, C*H*=CHCHOTMP), 5.53 (dd, *J* = 15.3, 9.0 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 14.1 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.4 (q, NC(*C*H$_3$)$_2$), 22.57 (t, *C*H$_2$CH$_3$), 25.18 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 28.19 (q, OC(*C*H$_3$)$_3$), 32.0 (t, *C*H$_2$CH$_2$CH$_3$), 33.9 (q, NC(*C*H$_3$)$_2$), 34.7 (t, TMPOCH*C*H$_2$), 34.9 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 41.7 (t, CH*C*H$_2$CH), 53.3 (d, CH*C*HCH=), 56.5

(d, *C*HCOO*t*Bu), 59.2 (s, N*C*$(CH_3)_2$), 60.4 (s, N*C*$(CH_3)_2$), 73.0 (d, *C*H(OH)CHCOO*t*Bu), 75.9 (d, HO*C*HCHCH=), 80.9 (s, O*C*$(CH_3)_3$), 84.54 (d, *C*HOTMP), 128.9 (d, *C*H=CHCHOTMP), 136.4 (d, =*C*HCHOTMP), 172.3 (s, COO*t*Bu).

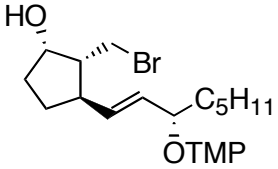
15β-**4-60**: ^{1}H NMR (400 MHz): δ = 0.84 (m, 3H, CH_2CH_3), 1.01-1.07 (m, 12H, NC(CH_3)$_2$), 1.15-1.55 (m, 14H, NCCH_2CH_2CH_2CN, $CH_2CH_2CH_2CH_2CH_3$, CH_2CHOTMP, O*H*), 1.38 (s, 9H, OC(CH_3)$_3$), 1.61 (m, 2H, CH_2CHOTMP, CHCH_2CH), 2.49 (m, 1H, CHCH_2CH), 2.86 (m, 1H, OHCHC*H*CH=), 3.00 (dd, *J* = 8.2, 4.5 Hz, 1H, C*H*COO*t*Bu), 4.00 (m, 1H, C*H*OTMP), 4.08 (m, 1H, HOC*H*CHCH=), 4.49 (m, 1H, C*H*(OH)CHCOO*t*Bu), 5.28 (m, 1H, C*H*=CHCHOTMP), 5.53 (dd, *J* = 15.4, 6.6 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 14.0 (q, CH_2CH_3), 17.3 (t, NCCH_2CH_2CH_2CN), 20.4 (q, NC(CH_3)$_2$), 22.61 (t, CH_2CH_3), 25.23 (t, $CH_2CH_2CH_2CH_3$), 28.24 (q, OC(CH_3)$_3$), 31.9 (t, $CH_2CH_2CH_3$), 33.9 (q, NC(CH_3)$_2$), 34.2 (t, TMPOCHCH_2), 34.9 (q, NC(CH_3)$_2$), 40.1 (t, NC$CH_2CH_2CH_2$CN), 42.0 (t, CHCH_2CH), 52.7 (d, CH*C*HCH=), 56.8 (d, *C*HCOO*t*Bu), 59.2 (s, N*C*$(CH_3)_2$), 60.4 (s, N*C*$(CH_3)_2$), 73.2 (d, *C*H(OH)CHCOO*t*Bu), 76.9 (d, HO*C*HCHCH=), 81.0 (s, O*C*$(CH_3)_3$), 84.48 (d, *C*HOTMP), 127.7 (d, *C*H=CHCHOTMP), 136.5 (d, =*C*HCHOTMP), 172.3 (s, COO*t*Bu).

6.9.4. Introduction of a leaving group

Bromination of diol 4-55:

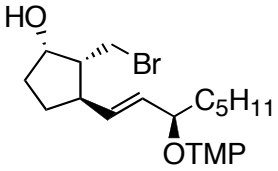
To a solution of a 2.2:1 mixture of diols **15α/β-4-55** (50 mg, 0.13 mmol) in 5 mL dry CH_2Cl_2 Ph_3P (68 mg, 0.26 mmol) was added at 0 °C. After stirring shortly CBr_4 (42 mg, 0.13 mmol) was added. The reaction mixture was warmed to r.t. and stirred for 15 h. The progress of the reaction was monitored by TLC (hexane/ethyl acetate 2:1 and 5:1). Dry methanol (7 mL) was added and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel. The solvent was evaporated and the residue (120 mg) was purified immediately on a short column (hexane/ethyl acetate 40:1, gradient to 2:1). First, **4-66** eluted at a polarity of 40:1, followed by a 2.7:1 mixture of **15α,β-4-65** at a polarity of 10:1. Yields: 30 mg (51%) **4-65** as a pale yellow oil and 20 mg (30%) **4-66** as a pale yellow oil. Two bromination experiments using IsoP **4-54**, performed similarly, gave complex mixtures. NMR spectra showed that decomposition occurred. The labile bromide **4-65** was immediately subjected to an alkylation reaction.

(*1S*,2R*,3R)-2-(Bromomethyl)-3-[(*1E,3S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15α-4-65:**



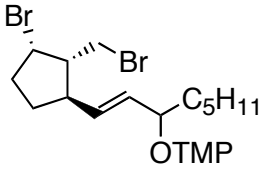
^{1}H NMR (200 MHz): δ = 0.87 (t, *J* = 6.3 Hz, 3H, CH_2CH_3), 1.10-1.71 (m, 28H, $NC(CH_3)_2$), $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$, CH_2CH_2CHOH), 1.85-2.17 (m, 3H, CH_2CHOH, CHCHCHOH), 2.36 (m, 1H, $CHCH_2Br$), 3.45 (m, 1H, CH_2Br), 3.66 (dd, *J* = 9.8, 4.1 Hz, 1H, CH_2Br), 4.05 (m, 1H, CHOTMP), 4.44 (m, 1H, CHOH), 5.20 (dd, *J* = 15.3, 8.2 Hz, 1H, CH=CH), 5.42 (dd, *J* = 15.3, 8.2 Hz, 1H, CH=CH). - ^{13}C NMR (50 MHz):
δ = 14.0 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.1 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.1 (t, $CH_2CH_2CH_2CH_3$), 31.1 (t, CH_2CH_2CHOH), 31.8 (t, $CH_2CH_2CH_2CH_3$), 32.2 (t, CH_2Br), 33.1 (t, CH_2CHOH), 34.0 (q, $NC(CH_3)_2$), 34.6 (t, $TMPOCHCH_2$), 35.1 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 45.4 (d, CH_2CHCH=), 54.2 (d, $CHCH_2Br$), 58.9 (s, $NC(CH_3)_2$), 60.1 (s, $NC(CH_3)_2$), 73.4 (d, CHOH), 84.8 (d, CHOTMP), 133.7 (d, CH=CH), 134.2 (d, CH=CH).

(*1S*,2R*,3R)-2-(Bromomethyl)-3-[(*1E,3R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ol 15β-4-65:**



15β-4-65, detectable resonances: ^{1}H NMR (200 MHz): δ = 2.36 (m, 1H, $CHCH_2Br$), 3.45 (m, 2H, CH_2Br), 4.03 (m, 1H, CHOTMP), 4.44 (m, 1H, CHOH), 5.20 (m, 2H, CH=CH). - ^{13}C NMR (50 MHz): δ = 133.5 (d, CH=CH), 134.2 (d, CH=CH).

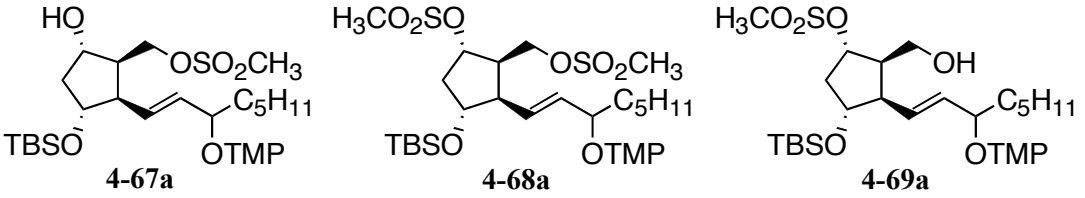
(*1S*,2S*,3R)-2-(Bromomethyl)-3-[(*1E,3S* and R**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentyl bromide 15α- and 15β-4-66:**



MS(EI) *m/z* (%): 348/350/352 (4) [M–TEMPOH$^+$], 260/271 (8) [M$^+$–TEMPO–Br], 213/215 (4), 189 (6), 157 (56) [TEMPOH]$^+$, 142 (100) [$TMPH_2^+$], 123 (12), 97 (12) [$C_7H_{15}^+$], 81 (12) [$C_6H_9^+$], 69 (26), 55 (20), 44 (14) [$C_3H_8^+$]. - **15α-4-66**: ^{1}H NMR (200 MHz): δ = 0.81 (t, *J* =

7.0 Hz, 3H, CH_2CH_3), 0.98-1.90 (m, 28H, $NC(CH_3)_2$), $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$, CH_2CH_2CHBr), 2.06 (m, 2H, CH_2CHBr, $CHCHCHBr$), 2.32 (m, 2H, CH_2CHBr, $CHCH_2Br$), 3.59 (A part of ABX, J = 10.6, 3.3 Hz, 1H, CH_2Br), 3.72 (B part of ABX, J = 10.4, 3.0 Hz, CH_2Br), 4.05 (m, 2H, $CHOTMP$, $CHBr$), 5.20 (dd, J = 15.3, 8.4 Hz, 1H, CH=CH), 5.45 (dd, J = 15.3, 8.6 Hz, 1H, CH=CH). - ^{13}C NMR (50 MHz):
δ = 14.0 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.0 (q, $NC(CH_3)_2$), 20.1 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.1 (t, $CH_2CH_2CH_2CH_3$), 31.5 (t, CH_2CH_2CHBr), 31.8 (t, $CH_2CH_2CH_3$), 34.0 (t, CH_2Br), 34.2 (q, $NC(CH_3)_2$), 34.6 (t, CH_2CHBr), 35.4 (t, $TMPOCHCH_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 44.3 (d, CH_2CHCH=), 51.2 (d, $CHCH_2Br$), 56.3 (d, $CHBr$), 59.0 (s, $NC(CH_3)_2$), 60.0 (s, $NC(CH_3)_2$), 84.7 (d, $CHOTMP$), 132.6 (d, CH=CH), 135.1 (d, CH=CH). - **15β-4-66**, assignable resonances: ^{1}H NMR (200 MHz): δ = 3.66 (m, 2H, CH_2Br), 4.05 (m, 2H, $CHOTMP$, $CHBr$), 5.34 (m, 2H, CH=CH).

Mesylation of 4-57:



4-67a **4-68a** **4-69a**

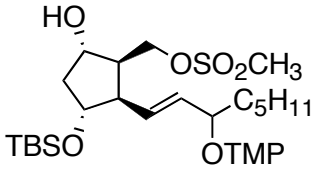
Method A: To a solution of **15α-4-57** (100 mg, 0.196 mmol) in 5 mL dry CH_2Cl_2, dry Et_3N (0.056 mL, 0.392 mmol) and MsCl (0.185 mL, 1*M* solution of in dry CH_2Cl_2, 0.185 mmol) were added subsequently slowly with good stirring at –50 °C. The reaction mixture was stirred at –50 °C for ca. 1.5 h. The progress of the reaction was monitored by TLC (hexane/ethyl acetate 2:1 and 5:1). Water (2 mL) was added and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, twice with saturated $NaHCO_3$ solution, and brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified immediately on a short column (hexane/ethyl acetate 10:1, gradient to pure ethyl acetate). First, **4-68a** and **4-69a** eluted as a mixture, followed by **4-67a** and unreacted **4-57** as a partly separable mixture. For yields see Table 6.6, entry 1.

Method B: The reaction was performed as above using **15α/β-4-57** (15α:15β = 3.1:1, 30 mg, 0.058 mmol), NEt_3 (0.016 mL, 0.116 mmol), and a 1*M* solution of MsCl in dry CH_2Cl_2 (0.063 mL, 0.063 mmol) at –20 °C for 2 h. The residue was purified immediately on a short column (hexane/ethyl acetate 10:1, gradient to 2:1). For yields see Table 6.6, entry 2.

Table 6.6 Yields of mesylation experiments with **4-57**

Entry	Method (Config. in 15-Pos.)	**4-67a** (%)	**4-68a** (%)	**4-69a** (%)	**4-57** (%)
1	A (α)	39.5 mg (34)	12 mg (9)	13 mg (17)	34.2 mg (34)
2	B (α:β = 3.1:1)	16.3 mg (48, α:β 3.8:1)	13.5 mg (35, α:β 5.3:1)	2.5 mg (7, α:β 1:1)	2.1 mg (7, α:β 1:2)

[(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3-[(*R* and S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-2-yl]methyl mesylate 15α- and 15β-4-67a:**

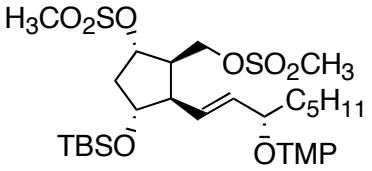


15α-**4-67a**: R_f (hexane/ethyl acetate 2:1) = 0.44. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.82 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 0.98-1.06 (m, 12H, NC(C*H*$_3$)$_2$), 1.18-1.47 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, TMPOCHC*H*$_2$), 1.64 (m, 2H, TMPOCHC*H*$_2$, CHC*H*$_2$CH), 2.24 (ddd, *J* = 14.5, 7.5, 4.7 Hz, 1H, CHC*H*$_2$CH), 2.59 (m, 1H, C*H*CH$_2$OSO$_2$), 2.80 (m, 1H, CHC*H*CH=), 2.94 (s, 3H, OSO$_2$C*H*$_3$), 3.89-4.03 (m, 3H, C*H*OH, C*H*OTBS, C*H*OTMP), 4.08 (A part of ABX system, *J* = 9.9, 8.5 Hz, 1H, CHC*H*$_2$OSO$_2$), 4.16 (B part of ABX system, *J* = 10.0, 6.4 Hz, 1H, CHC*H*$_2$OSO$_2$), 4.99 (dd, *J* = 15.3, 10.0 Hz, 1H, C*H*=CHCHOTMP), 5.46 (dd, *J* = 15.3, 8.4 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.04 (q, CH$_2$*C*H$_3$), 17.2 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 31.94 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.5 (t, *C*H$_2$CHOTMP), 35.4 (q, NC(*C*H$_3$)$_2$), 37.5 (q, OSO$_2$*C*H$_3$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.8 (t, CH*C*H$_2$CH), 50.0 (d, *C*HCH$_2$OSO$_2$), 53.4 (d, CH*C*HCH=), 59.0 (s, N*C*(CH$_3$)$_2$), 60.1 (s, N*C*(CH$_3$)$_2$), 69.8 (t, *C*H$_2$OSO$_2$), 75.1 (d, *C*HOH), 77.8 (d, *C*HOTBS), 84.7 (d, *C*HOTMP), 126.8 (d, *C*H=CHCHOTMP), 137.5 (d, =*C*HCHOTMP).

15β-**4-67a** detectable resonances: ^{1}H NMR (400 MHz): δ = –0.02 (s, 6H, Si(C*H*$_3$)$_2$), 2.19 (m, 1H, CHC*H*$_2$CH), 2.59 (m, 1H, C*H*CH$_2$OSO$_2$), 2.74 (m, 1H, CHC*H*CH=), 2.97 (s, 3H, OSO$_2$C*H*$_3$), 3.89-4.18 (m, 4H, C*H*OH, C*H*OTBS, C*H*OTMP, CHC*H*$_2$OSO$_2$), 4.30 (B part of ABX system, *J* = 10.1, 5.7 Hz, 1H, CHC*H*$_2$OSO$_2$), 5.06 (dd, *J* = 15.3, 9.9 Hz, 1H, C*H*=CHCHOTMP), 5.46 (m, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q,

Si(CH_3)$_2$), –4.8 (q, Si(CH_3)$_2$), 14.00 (q, CH_2CH_3), 31.89 (t, $CH_2CH_2CH_3$), 34.4 (t, CH_2CHOTMP), 37.6 (q, OSO_2CH_3), 42.9 (t, CHCH_2CH), 49.8 (d, CHCH$_2$OSO$_2$), 53.2 (d, CHCHCH=), 70.0 (t, CH_2OSO_2), 74.9 (d, CHOH), 78.0 (d, CHOTBS), 84.4 (d, CHOTMP), 127.6 (d, CH=CHCHOTMP), 137.1 (d, =CHCHOTMP).

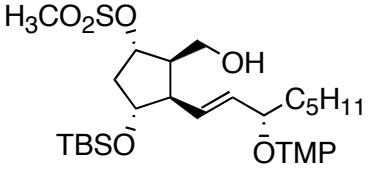
[(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-1-(mesyloxy)-3-[(*R*,E and S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-2-yl]methyl mesylate 15α- and 15β-4-68a:**



15α-4-68a: R_f (hexane/ethyl acetate 2:1) = 0.65. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(CH_3)$_2$), 0.82 (s+m, 12H, SiC(CH_3)$_3$, CH_2CH_3), 0.98-1.09 (m, 12H, NC(CH_3)$_2$), 1.21-1.62 (m, 14H, NCCH_2CH_2CH_2CN, CH_2CH_2CH_2CH_2CH$_3$), 1.89 (m, 1H, CHCH_2CH), 2.53 (m, 1H, CHCH_2CH), 2.77 (m, 1H, CHCHCH=), 2.88 (quint, *J* = 7.0 Hz, 1H, CHCH$_2$OSO$_2$), 2.95 (s, 3H, OSO_2CH_3), 2.98 (s, 3H, OSO_2CH_3), 3.94 (dt, *J* = 8.1, 5.0 Hz, 1H, CHOTMP), 4.01 (dt, *J* = 5.6, 2.8 Hz, 1H, CHOTBS), 4.18 (AB part of ABX system, *J* = 10.1, 7.3, 6.5 Hz, 2H, CHCH_2OSO$_2$), 4.90 (m, 1H, CHOSO$_2$), 5.02 (dd, *J* = 15.3, 9.7 Hz, 1H, CH=CHCHOTMP), 5.53 (dd, *J* = 15.4, 8.6 Hz, 1H, =CHCHOTMP). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(CH_3)$_2$), –4.7 (q, Si(CH_3)$_2$), 14.0 (q, CH_2CH_3), 17.2 (t, NCCH$_2$CH$_2$CH$_2$CN), 17.9 (s, SiC(CH$_3$)$_3$), 20.3 (q, NC(CH$_3$)$_2$), 20.4 (q, NC(CH$_3$)$_2$), 22.5 (t, CH_2CH_3), 25.2 (t, $CH_2CH_2CH_2CH_3$), 25.73 (q, SiC(CH$_3$)$_3$), 31.9 (t, $CH_2CH_2CH_3$), 34.3 (q, NC(CH$_3$)$_2$), 34.4 (t, CH_2CHOTMP), 35.3 (q, NC(CH$_3$)$_2$), 37.3 (q, OSO_2CH_3), 38.4 (q, OSO_2CH_3), 40.2 (t, NCCH$_2$CH$_2$CH$_2$CN), 41.4 (t, CHCH_2CH), 46.5 (d, CHCH$_2$OSO$_2$), 52.7 (d, CHCHCH=), 59.1 (s, NC(CH$_3$)$_2$), 60.2 (s, NC(CH$_3$)$_2$), 68.4 (t, CH_2OSO_2), 75.7 (d, CHOTBS), 81.5 (d, CHOSO$_2$), 84.5 (d, CHOTMP), 125.7 (d, CH=CHCHOTMP), 138.5 (d, =CHCHOTMP).

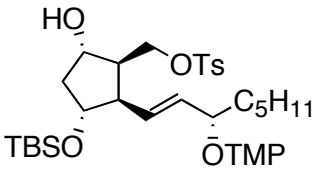
15β-4-68a, detectable resonances: ^{1}H NMR (400 MHz): δ = 4.29 (AB part of ABX system, *J* = 10.1, 6.7, 5.1 Hz, 2H, CHCH_2OSO$_2$), 5.10 (dd, *J* = 15.3, 9.1 Hz, 1H, CH=CHCHOTMP). - ^{13}C NMR (100 MHz): δ = 25.69 (q, SiC(CH$_3$)$_3$), 52.4 (d, CHCHCH=), 68.5 (t, CH_2OSO_2), 75.8 (d, CHOTBS), 81.3 (d, CHOSO$_2$), 126.7 (d, CH=CHCHOTMP), 138.3 (d, =CHCHOTMP).

(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-3-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-1-yl mesylate 15α-4-69a:**

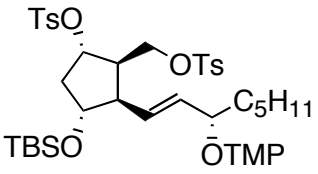


^{1}H NMR (400 MHz): δ = –0.001 (s, 3H, Si(C*H*$_3$)$_2$), 0.004 (s, 3H, Si(C*H*$_3$)$_2$), 0.81 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 1.00-1.13 (m, 12H, NC(C*H*$_3$)$_2$), 1.15-1.62 (m, 14H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.88 (m, 1H, CHC*H*$_2$CH), 2.51 (m, 2H, CHC*H*$_2$CH, C*H*CH$_2$OH), 2.75 (m, 1H, CHC*H*CH=), 2.97 (s, 3H, OSO$_2$C*H*$_3$), 3.65 (m, 2H, C*H*$_2$OH), 4.09 (m, 2H, C*H*OTMP, C*H*OTBS), 4.95 (m, 1H, C*H*OSO$_2$), 5.36 (dd, *J* = 15.6, 7.2 Hz, 1H, C*H*=CHCHOTMP), 5.53 (dd, *J* = 15.4, 8.7 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.8 (q, Si(*C*H$_3$)$_2$), –4.4 (q, Si(*C*H$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.8 (s, Si*C*(CH$_3$)$_3$), 20.5 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 22.6 (t, *C*H$_2$CH$_3$), 25.3 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 34.1 (q, NC(*C*H$_3$)$_2$), 34.3 (q, NC(*C*H$_3$)$_2$), 34.6 (t, *C*H$_2$CHOTMP), 38.2 (q, OSO$_2$*C*H$_3$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 41.5 (t, CH*C*H$_2$CH), 49.2 (d, *C*HCH$_2$OH), 50.8 (d, CH*C*HCH=), 59.1 (s, N*C*(CH$_3$)$_2$), 59.3 (s, N*C*(CH$_3$)$_2$), 61.0 (t, *C*H$_2$OH), 74.0 (d, *C*HOTBS), 82.1 (d, *C*HOSO$_2$), 84.5 (d, *C*HOTMP), 129.2 (d, *C*H=CHCHOTMP), 135.0 (d, =*C*HCHOTMP).

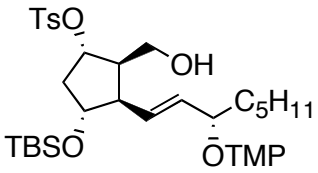
Tosylation of 15α**-4-57:**



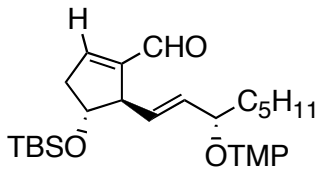
4-67b



4-68b



4-69b



Enal

Method A: To a solution of **15α-4-57** (30 mg, 0.059 mmol) in 4 mL dry CH_2Cl_2, dry Et_3N (0.035 mL, 0.25 mmol) and 1 mL of a freshly prepared 0.063*M* solution of TsCl in dry CH_2Cl_2 (12 mg, 0.063 mmol) were added subsequently very slowly with good stirring via syringe at –80 °C. A spatula tip of DMAP was added, the reaction mixture was stirred at –78 °C for ca. 30 min, warmed to –20 °C during 3 h and subsequently to 0 °C during 2.5 h. The reaction, which was not complete by TLC, was hydrolysed with 5 mL water and diluted with

diethyl ether. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 40 mg of a crude product, which was purified immediately on a short column (hexane/ethyl acetate 10:1, gradient to 2:1). For yields, see Table 6.7, entry 1.

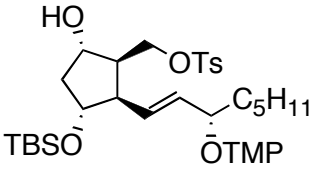
Method B: The reaction was performed under similar conditions with 50 mg (0.098 mmol) of **15α-4-57**, 20 mg (0.104 mmol) TsCl, and 0.027 mL (0.194 mmol) of Et_3N. The mixtures was stirred at 0 °C for 2.5 h. The crude product was purified immediately on a short column (hexane/ethyl acetate 10:1, gradient to 2:1). For yields, see Table 6.7, entry 2.

Method C: The reaction was performed under similar conditions with 40 mg (0.078 mmol) of **15α-4-57,** 0.02 mL (0.14 mmol) of Et_3N, and 20 mg (0.105 mmol) of TsCl at 0 °C for 0.5 h and stirred at room temperature for 28 h, after which it was not complete by TLC. Another 0.02 mL (0.14 mmol) of Et_3N and 12 mg (0.06 mmol) of TsCl were added and stirring was continued for additional 24 h. Workup was performed similarly as above and the crude product was purified immediately on a short column (hexane/ethyl acetate 10:1, gradient to 2:1). For yields, see Table 6.7, entry 3.

Table 6.7 Tosylation of Diol **15α-4-57.**

Entry	Method	**4-67b** (%)	**4-68b** (%)	**4-69b** (%)	**15α-4-57** (%)	**Enal**
1	A	10 mg (25)	- (0)	2 mg (5)	20 mg (67)	- (0)
2	B	10 mg (15)	8 mg (10)	2 mg (3)	14 mg (28)	traces
3	C	10 mg (19)	30 mg (47)	- (0)	5 mg (12)	8 mg (22)

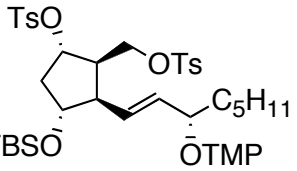
[(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-2-yl]methyl tosylate 15α-67b:**



R_f (hexane/ethyl acetate 2:1) = 0.59. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.82 (s, 9H, SiC(C*H*$_3$)$_3$), 0.83 (m, 3H, CH$_2$C*H*$_3$), 0.98-1.12 (m, 12H, NC(C*H*$_3$)$_2$), 1.14-1.29 (m, 7H, NCCH$_2$C*H*$_2$CH$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.31-1.42 (m, 5H, TMPOCHC*H*$_2$, NCC*H*$_2$CH$_2$C*H*$_2$CN), 1.55 (m, 2H, NCCH$_2$C*H*$_2$CH$_2$CN, TMPOCHC*H*$_2$), 1.63 (m, 1H, CHC*H*$_2$CH), 2.22 (m, 1H, CHC*H*$_2$CH), 2.40 (s, 3H, C$_6$H$_4$C*H*$_3$), 2.49 (m, 1H, C*H*CH$_2$OSO$_2$), 2.76 (m, 1H, CHC*H*CH=), 3.88-4.06 (m, 5H, CHC*H*$_2$OSO$_2$, C*H*OH, C*H*OTBS, C*H*OTMP), 4.96 (dd, *J* = 15.3, 9.3 Hz, 1H, C*H*=CHCHOTMP), 5.43 (dd, *J* = 15.3, 8.4 Hz, 1H,

=C*H*CHOTMP), 7.28 (d, *J* = 8.1 Hz, 2H, arom. *H*), 7.73 (d, *J* = 8.3 Hz, 2H, arom. *H*). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 14.1 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.3 (q, NC(*C*H$_3$)$_2$), 21.6 (q, OSO$_2$C$_6$H$_4$*C*H$_3$), 22.5 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 32.0 (t, *C*H$_2$CH$_2$CH$_3$), 34.0 (q, NC(*C*H$_3$)$_2$), 34.6 (t, *C*H$_2$CHOTMP), 35.3 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 42.9 (t, CH*C*H$_2$CH), 49.9 (d, *C*HCH$_2$OSO$_2$), 53.3 (d, CH*C*HCH=), 60.2 (s, N*C*(CH$_3$)$_2$), 70.4 (t, *C*H$_2$OSO$_2$), 75.1 (d, *C*HOH), 77.7 (d, *C*HOTBS), 84.7 (d, *C*HOTMP), 126.9 (d, *C*H=CHCHOTMP), 127.8 (d, *C*H arom.), 129.8 (d, *C*H arom.), 133.2 (s, *C*SO$_2$), 137.3 (d, =*C*HCHOTMP), 144.7 (s, *C*CH$_3$). - IR (Film): $\tilde{\nu}$ = 3443 (w), 2929 (s), 2858 (m), 1467 (w), 1364 (m), 1257 (w), 1179 (m), 1100 (w), 959 (m), 839 (m), 816 (w), 779 (m), 667 (w) cm^{-1}. - MS(ESI) *m/z* (%): 666 (100) [M+H$^+$], 158 (9) [TEMPOH$_2^+$]. - HRMS: $C_{36}H_{64}NO_6SSi^+$: calc. 666.4224; found 666.4230.

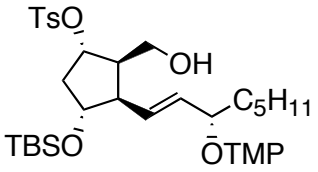
[(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-3-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-1-(tosyloxy)cyclopent-2-yl]methyl tosylate 15α-4-68b:**



R$_f$ (hexane/ethyl acetate 2:1) = 0.75. - ^{1}H NMR (200 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.85 (s, 9H, SiC(C*H*$_3$)$_3$), 0.90 (m, 3H, CH$_2$C*H*$_3$), 1.04-1.78 (m, 27H, NC(C*H*$_3$)$_2$, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, CHC*H*$_2$CH), 2.36 (m, 1H, CHC*H*$_2$CH), 2.48 (s, 6H, C$_6$H$_4$C*H*$_3$), 2.67 (m, 2H, CHC*H*CH=, C*H*CH$_2$OSO$_2$), 4.02 (m, 4H, C*H*OTMP, C*H*OTBS, CHC*H*$_2$OSO$_2$), 4.63 (m, 1H, C*H*OSO$_2$), 4.95 (dd, *J* = 15.6, 8.6 Hz, 1H, C*H*=CHCHOTMP), 5.52 (dd, *J* = 15.4, 8.7 Hz, 1H, =C*H*CHOTMP), 7.36 (dd, *J* = 8.0, 0.5 Hz, 4H, arom. *H*), 7.77 (m, 4H, arom. *H*). - ^{13}C NMR (50 MHz): δ = –4.6 (q, Si(*C*H$_3$)$_2$), –4.5 (q, Si(*C*H$_3$)$_2$), 14.3 (q, CH$_2$*C*H$_3$), 17.5 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.1 (s, Si*C*(CH$_3$)$_3$), 20.5 (q, NC(*C*H$_3$)$_2$), 20.6 (q, NC(*C*H$_3$)$_2$), 21.85 (q, OSO$_2$C$_6$H$_4$*C*H$_3$), 21.86 (q, OSO$_2$C$_6$H$_4$*C*H$_3$), 22.8 (t, *C*H$_2$CH$_3$), 25.4 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.0 (q, SiC(*C*H$_3$)$_3$), 32.1 (t, *C*H$_2$CH$_2$CH$_3$), 34.3 (q, NC(*C*H$_3$)$_2$), 34.8 (t, *C*H$_2$CHOTMP), 35.5 (q, NC(*C*H$_3$)$_2$), 40.4 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 41.1 (t, CH*C*H$_2$CH), 47.1 (d, *C*HCH$_2$OSO$_2$), 52.1 (d, CH*C*HCH=), 59.3 (s, N*C*(CH$_3$)$_2$), 60.3 (s, N*C*(CH$_3$)$_2$), 68.5 (t, *C*H$_2$OSO$_2$), 75.8 (d, *C*HOTBS), 82.1 (d, *C*HOSO$_2$), 84.7 (d, *C*HOTMP), 126.1 (d, *C*H=CHCHOTMP), 128.06 (d, *C*H arom.), 128.1 (d, *C*H arom.), 130.07 (d, *C*H arom.), 130.09 (d, *C*H arom.), 133.2 (s, *C*SO$_2$), 134.0 (s, *C*SO$_2$), 138.5 (d, =*C*HCHOTMP),

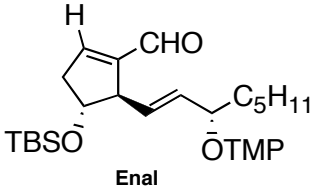
145.0 (s, *C*CH_3). - IR (Film): $\tilde{\nu}$ = 2928 (m), 2857 (w), 1361 (m), 1189 (m), 1176 (s), 1097 (m), 957 (w), 835 (s), 813 (m), 777 (m), 665 (w) cm^{-1}. - MS(ESI) *m/z* (%): 820 (100) [$M+H^+$], 686 (32) [$M+Na^+$–TEMPO], 582 (10), 492 (8) [M–TEMPO–TsO]. - HRMS: $C_{43}H_{70}NO_8S_2Si^+$: calc. 820.4312; found 820.4306.

(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-3-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-1-yl tosylate 15α-4-69b:**



R_f (hexane/ethyl acetate 2:1) = 0.68. - ^{1}H NMR (200 MHz): δ = –0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.83 (s, 9H, SiC(C*H*$_3$)$_3$), 0.88 (m, 3H, CH_2CH_3), 1.04-1.10 (m, 12H, NC(C*H*$_3$)$_2$), 1.26-1.79 (m, 15H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, CHC*H*$_2$CH), 2.31 (m, 1H, CHC*H*$_2$CH), 2.45 (s, 3H, $C_6H_4CH_3$), 2.57 (m, 1H, C*H*CH_2OH), 2.73 (m, 1H, CHC*H*CH=), 3.53 (m, 2H, CHC*H*$_2$OH), 4.04 (m, 2H, C*H*OTMP, C*H*OTBS), 4.81 (m, 1H, C*H*OSO_2), 5.48 (m, 2H, C*H*=C*H*CHOTMP), 7.34 (m, 2H, arom. *H*), 7.79 (m, 2H, arom. *H*).

(*4R*,5R)-4-(*tert*-Butyldimethylsilyloxy)-5-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentenecarbaldehyde:**

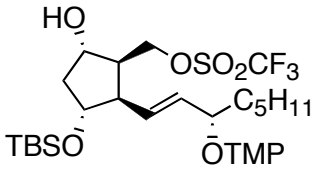


Enal

R_f (hexane/ethyl acetate 2:1) = 0.85. - ^{1}H NMR (200 MHz): δ = –0.07 (s, 3H, Si(C*H*$_3$)$_2$), 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (s+m, 12H, SiC(C*H*$_3$)$_3$+CH_2CH_3), 0.96-1.51 (m, 26H, NC(C*H*$_3$)$_2$, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 2.39 (m, 1H, CHC*H*$_2$CH), 2.82 (m, 1H, CHC*H*$_2$CH), 3.41 (m, 1H, CHC*H*CH=), 3.90 (dt, *J* = 8.3, 4.4 Hz, 1H, C*H*OTMP), 4.21 (m, 1H, C*H*OTBS), 5.21 (dd, *J* = 15.6, 7.3 Hz, 1H, C*H*=CHCHOTMP), 5.37 (dd, *J* = 15.4, 7.9 Hz, 1H, =C*H*CHOTMP), 6.75 (br. s, 1H, C*H*=CCHO), 9.68 (s, 1H, C*H*O).

[(*1S*,2R*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-2-yl]methyl triflate**

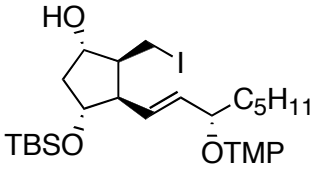
15α-4-67c:



To a solution of 15α-**4-57** (70 mg, 0.137 mmol) in 3 mL dry CH_2Cl_2, dry 2,6-lutidine (0.052 mL, 0.44 mmol) and fresh triflic anhydride (0.022 mL, 0.137 mmol) were added subsequently slowly via syringe with good stirring at –78 °C. The reaction mixture was stirred at –78 °C for ca. 2.5 h and monitored by TLC (R_f(**15α-4-67c** hexane/ethyl acetate 5:1) = 0.50). A spatula tip of DMAP was added at –78 °C, the reaction was stirred for another 30 min and allowed to warm to –20 °C during 2.5 h. Although not complete by TLC, the reaction was quenched with 10 mL of water at –80 °C and diluted with 5 mL of diethyl ether. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed twice with $NaHCO_3$ solution, twice with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 90 mg of crude product, which was purified immediately on a short column (hexane/ethyl acetate 20:1, gradient to 2:1) to give **15α-4-67c** (35 mg, 40%) and diol **4-57** (20 mg, 28%). Colourless unstable oil, which was used immediately for the next step.

R_f (hexane/ethyl acetate 5:1) = 0.50. - ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.81 (m+s, 12H, CH_2CH_3, SiC(C*H*$_3$)$_3$), 0.90-1.02 (m, 12H, NC(C*H*$_3$)$_2$), 1.19-1.41 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$CHOTMP), 1.63 (m, 2H, CHC*H*$_2$CH, C*H*$_2$CHOTMP), 2.23 (d, *J* = 8.8 Hz, 1H, OH), 2.26 (m, 1H, CHC*H*$_2$CH), 2.67 (dq, *J* = 5.1, 7.5 Hz, 1H, C*H*CH$_2$OSO$_2$CF$_3$), 2.80 (m, 1H, C*H*CHOTBS), 3.95 (m, 3H, C*H*OTBS, C*H*OH, C*H*OTMP), 4.44 (d, *J* = 7.2 Hz, 2H, C*H*$_2$OSO$_2$CF$_3$), 4.94 (dd, *J* = 15.2, 10.0 Hz, 1H, C*H*=CHCHOTMP), 5.49 (dd, *J* = 15.1, 8.7 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.9 (q, Si(C*H*$_3$)$_2$), –4.7 (q, Si(C*H*$_3$)$_2$), 14.0 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 17.9 (s, Si*C*(CH$_3$)$_3$), 20.3 (q, NC(*C*H$_3$)$_2$), 22.5 (t, *C*H$_2$CH$_3$), 25.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 33.9 (q, NC(*C*H$_3$)$_2$), 34.5 (t, *C*H$_2$CHOTMP), 35.6 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.0 (t, CH*C*H$_2$CH), 50.3 (d, *C*HCH$_2$OSO$_2$CF$_3$), 53.4 (d, *C*HCHOTBS), 60.2 (s, N*C*(CH$_3$)$_2$), 74.6 (d, *C*HOH), 77.0 (t, *C*H$_2$OTf), 77.6 (d, *C*HOTBS), 84.7 (d, *C*HOTMP), 126.0 (d, *C*H=CHCHOTMP), 138.4 (d, =*C*HCHOTMP).

[(*1S*,2S*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3-[(*S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopent-2-yl]methyl iodide 15α-4-70:**

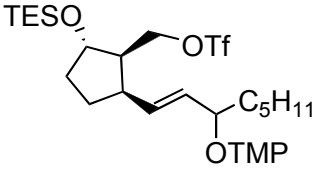


A mixture of flame-dried NaI (120 mg, 0.8 mmol), a spatula tip of activated powdered molecular sieves 4Å, a spatula tip of K_2CO_3, **15α-4-67a** (39.5 mg, 0.067 mmol), **15α-4-69a** (6.3 mg, 0.0106 mmol) and diol **15α-4-57** (34.2 mg (0.067 mmol) in 2.5 mL ethyl methyl ketone was heated with stirring at 80 °C for 1 h and at 60 °C for 1.5 h. Column chromatography of the crude mixture (hexane/ethyl acetate 10:1, gradient to 5:1) gave 30 mg (72%) of **15α-4-70** and 30 mg of unchanged diol **15α-4-57**. Colourless oil, which was used without further characterisation in the next step.

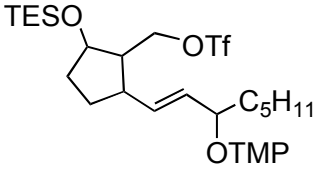
R_f(hexane/ethyl acetate 2:1) = 0.80. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.81 (s+m, 12H, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 0.99-1.13 (m, 12H, NC(C*H*$_3$)$_2$), 1.15-1.59 (m, 13H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, TMPOCHC*H*$_2$), 1.62-1.72 (m, 2H, TMPOCHC*H*$_2$, CHC*H*$_2$CH), 2.03 (d, *J* = 8.2 Hz, 1H, O*H*), 2.36 (ddd, *J* = 14.4, 8.1, 4.9 Hz, 1H, CHC*H*$_2$CH), 2.63 (m, 1H, C*H*CH$_2$I), 2.78 (m, 1H, CHC*H*CH=), 2.91 (t, *J* = 9.4 Hz, 1H, C*H*$_2$I), 3.23 (dd, *J* = 9.5, 7.2 Hz, 1H, C*H*$_2$I), 3.88 (m, 1H, C*H*OTBS), 3.91 (dt, *J* = 4.6, 8.7 Hz, 1H, C*H*OTMP), 4.02 (m, 1H, C*H*OH), 4.91 (dd, *J* = 15.2, 10.1 Hz, 1H, C*H*=CHCHOTMP), 5.53 (dd, *J* = 15.2, 8.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.9 (q, Si(*C*H$_3$)$_2$), –4.7 (q, Si(*C*H$_3$)$_2$), 6.2 (t, *C*H$_2$I), 14.1 (q, CH$_2$*C*H$_3$), 17.3 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.0 (s, Si*C*(CH$_3$)$_3$), 20.4 (q, NC(*C*H$_3$)$_2$), 22.7 (t, *C*H$_2$CH$_3$), 25.2 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 33.9 (q, NC(*C*H$_3$)$_2$), 34.6 (t, *C*H$_2$CHOTMP), 35.6 (q, NC(*C*H$_3$)$_2$), 40.2 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 43.9 (t, CH*C*H$_2$CH), 53.7 (d, *C*HCH$_2$I), 55.6 (d, CH*C*HCH=), 58.9 (s, N*C*(CH$_3$)$_2$), 60.2 (s, N*C*(CH$_3$)$_2$), 77.1 (d, *C*HOH), 77.6 (d, *C*HOTBS), 85.2 (d, *C*HOTMP), 126.3 (d, *C*H=CHCHOTMP), 140.0 (d, =*C*HCHOTMP).

Minor 15-Isomer: ^{1}H NMR (400 MHz): δ = 3.14 (t, *J* = 9.4 Hz, 1H, C*H*$_2$I), 3.24 (dd, *J* = 9.7, 7.0 Hz, 1H, C*H*$_2$I), 4.02 (m, 1H, C*H*OH), 5.06 (dd, *J* = 15.2, 9.8 Hz, 1H, C*H*=CHCHOTMP), 5.49 (dd, *J* = 15.2, 8.8 Hz, 1H, =C*H*CHOTMP).

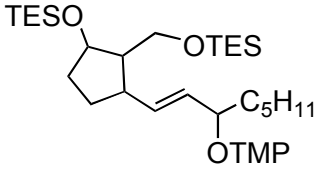
[(*1R*,2R*,5S)-2-[(*1E,3R** and *S**)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-5-(triethylsilyloxy)cyclopent-1-yl]methyl trifluoromethanesulfonate 15α- and 15β-4-71:**



15α/β-**4-71**



4-72-I_{3-2}



4-71TES$_2$

To a solution of diol **4-54** (160 mg, 0.42 mmol, R_f(hexane/ethyl acetate 2:1) = 0.15) in 5 mL of dry CH_2Cl_2 dry 2,6-lutidine (0.147 mL, 1.26 mmol, 3 equiv.) was added via syringe at –78 °C. After stirring the solution shortly, fresh triflic anhydride (73 μl, 0.44 mmol, 1.05 equiv.) was added very slowly under good stirring and the reaction mixture was stirred at –78 °C for ca. 30 min until complete by TLC (R_f of the sulfonylated alcohol (hexane/ethyl acetate 2:1) = 0.51 and (hexane/ethyl acetate 5:1) = 0.32). Two smaller spots were also observed on TLC with (hexane/ethyl acetate 2:1) = 0.62, 0.75. The reaction was quenched at –78 °C with 10 mL water, diluted with diethyl ether and warmed to r.t. in 10 min. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 200 mg of crude product. This was dissolved in diethyl ether and transferred to a different flask, weight 185 mg. The crude product was dissolved in 5 mL dry CH_2Cl_2 and dry 2,6-lutidine (0.126 mL, 1.08 mmol, 3 equiv.) was added via syringe at –78 °C. Subsequently triethylsilyl triflate (0.122 mL, 0.54 mmol, 1.5 equiv.) was added at –78 °C and the reaction was stirred at this temperature for 30 min. The consumption was monitored by TLC (hexane/ethyl acetate 10:1 and 20:1). The reaction was quenched at –80 °C with 10 mL water, diluted with 20 mL diethyl ether and warmed to r.t. in 10 min. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed twice with $NaHCO_3$ solution, twice with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 200 mg of crude product. It was purified immediately on a short column (hexane/ethyl acetate 20:1, gradient to 10:1) to give 140 mg of an inseparable mixture of 15α–**4-71**/15β–**4-71**/**4-72**-I_{3-2}/**4-71TES$_2$** (5:1:trace:2) as a colourless oil, R_f (hexane/ethyl acetate 10:1) = 0.41. Yield: **4-71** 106 mg (47%); **4-71TES$_2$** 34 mg (15%).

15α-/15β-**4-71:** IR (Film): $\tilde{\nu}$ = 2953 (m), 2932 (s), 2875 (m), 1462 (w), 1416 (m), 1376 (w), 1360 (w), 1243 (m), 1209 (m), 1147 (m), 1131 (w), 1086 (m), 1006 (m), 974 (m), 936 (s), 809 (w), 740 (s), 727 (s). - MS(ESI) *m/z* (%): 996 (10), 974 (25), 842 (24), 629 (37) [$M+H^+$], 628 (91) [M^+], 610 (84) [**4-71TES$_2$**$^+$], 496 (78) [M–TEMPO+H+Na^+ or M^+–OTES], 478 (100)

$[M^+–CF_3SO_2OH]$, 364 (13) $[M–OTES–TEMPO+H+Na]^+$, 158 (63) $[TEMPOH_2]^+$, 144 (13). - HRMS: $C_{30}H_{57}F_3NO_5SSi^+$: calc. 628.3679; found 728.3681.

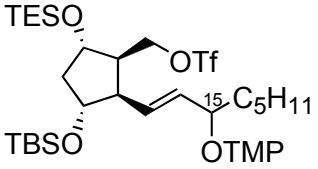
15α-IsoP-**4-71**: ^{1}H NMR (400 MHz, C_6D_6): δ = 0.56 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.93 (m, 3H, CH$_2$CH$_2$C*H*$_3$), 0.97-1.10 (m, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.17-1.59 (m, 26H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, NC(C*H*$_3$)$_2$, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$, C*H*$_2$C*H*$_2$CHOTES), 1.60 (m, 1H, C*H*$_2$CHOTMP), 1.70-1.95 (m, 3H, C*H*$_2$C*H*$_2$CHOTES, C*H*$_2$CHOTMP), 2.22 (m, 1H, C*H*CH$_2$OSO$_2$CF$_3$), 2.76 (dt, *J* = 15.7, 7.9 Hz, 1H, CH$_2$C*H*CH=), 3.98 (dd, *J* = 11.6, 5.5 Hz, 1H, C*H*OTES), 4.19 (m, 1H, C*H*OTMP), 4.27 (m, 1H, C*H*$_2$OSO$_2$CF$_3$), 4.49 (dt, *J* = 9.7, 6.8 Hz, 1H, C*H*$_2$OSO$_2$CF$_3$), 5.24 (dd, *J* = 15.3, 8.3 Hz, 1H, C*H*=CHCHOTMP), 5.43 (dd, *J* = 15.3, 8.6 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 5.1 (t, Si*C*H$_2$), 7.1 (q, SiCH$_2$*C*H$_3$), 14.30 (q, CH$_2$CH$_2$C*H*$_3$), 17.8 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.6 (q, NC(*C*H$_3$)$_2$), 20.8 (q, NC(*C*H$_3$)$_2$), 23.0 (t, CH$_2$C*H*$_2$CH$_3$), 25.7 (t, C*H*$_2$CH$_2$CH$_2$CH$_3$), 28.4 (t, *C*H$_2$CH$_2$CHOTES), 32.45 (t, C*H*$_2$CH$_2$CH$_3$), 34.0 (t, *C*H$_2$CHOTES), 34.5 (q, NC(*C*H$_3$)$_2$), 35.0 (t, *C*H$_2$CHOTMP), 35.8 (q, NC(*C*H$_3$)$_2$), 40.7 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 41.9 (d, CH$_2$*C*HCH=), 52.0 (d, *C*HCH$_2$OSO$_2$CF$_3$), 59.3 (s, N*C*(CH$_3$)$_2$), 60.5 (s, N*C*(CH$_3$)$_2$), 74.7 (d, *C*HOTES), 77.3 (t, *C*H$_2$OTf), 85.3 (d, *C*HOTMP), 117.8 (q, CF$_3$), 130.6 (d, *C*H=CHCHOTMP), 135.9 (d, =*C*HCHOTMP).

15β-IsoP-**4-71**, detectable resonances: ^{1}H NMR (400 MHz, C_6D_6): δ = 1.60 (m, 1H, C*H*$_2$CHOTMP), 1.70-1.95 (m, 3H, C*H*$_2$C*H*$_2$CHOTES, C*H*$_2$CHOTMP), 2.29 (m, 1H, C*H*CH$_2$OSO$_2$CF$_3$), 2.82 (m, CH$_2$C*H*CH=), 4.08 (m, 1H, C*H*OTES), 4.19 (m, 1H, C*H*OTMP), 4.27 (m, 1H, C*H*$_2$OSO$_2$CF$_3$), 4.57 (m, 1H, C*H*$_2$OSO$_2$CF$_3$), 5.24 (m, 1H, C*H*=CHCHOTMP), 5.43 (m, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 4.9 (t, Si*C*H$_2$), 7.18 (q, SiCH$_2$*C*H$_3$), 14.34 (q, CH$_2$CH$_2$C*H*$_3$), 17.7 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 20.6 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 23.1 (t, CH$_2$C*H*$_2$CH$_3$), 25.9 (t, C*H*$_2$CH$_2$CH$_2$CH$_3$), 32.38 (t, C*H*$_2$CH$_2$CH$_3$), 35.1 (t, *C*H$_2$CHOTMP), 36.2 (q, NC(*C*H$_3$)$_2$), 40.7 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 41.9 (d, CH$_2$*C*HCH=), 55.9 (d, *C*HCH$_2$OSO$_2$CF$_3$), 75.0 (d, *C*HOTES), 77.5 (t, *C*H$_2$OTf), 85.6 (d, *C*HOTMP), 133.7 (d, *C*H=CHCHOTMP).

4-72-I$_{3\text{-}2}$ (detectable resonances): ^{1}H NMR (400 MHz, C_6D_6): δ = 4.34 (m, 1H, C*H*$_2$OSO$_2$CF$_3$), 4.46 (m, 1H, C*H*$_2$OSO$_2$CF$_3$).

4-71TES$_2$ (detectable resonances): ^{1}H NMR (400 MHz, C_6D_6): δ = 0.61-0.71 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 3.12 (m, CH$_2$C*H*CH=), 3.53 (m, 1H, C*H*$_2$OTES), 3.80 (m, 1H, C*H*$_2$OTES), 4.19 (m, 1H, C*H*OTMP), 4.41 (m, 1H, C*H*OTES), 5.47-5.65 (m, 2H, C*H*=C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 5.4 (t, Si*C*H$_2$), 7.2 (q, SiCH$_2$*C*H$_3$), 42.8 (d, CH$_2$*C*HCH=), 62.0 (t, *C*H$_2$OTES), 75.9 (d, *C*HOTES), 85.8 (d, *C*HOTMP), 133.0 (d, *C*H=CHCHOTMP), 134.0 (d, =*C*HCHOTMP).

[(*1R*,2R*,3R*,5S)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*1E,3R** and *S**)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-5-(triethylsilyloxy)cyclopent-1-yl]methyl trifluoromethanesulfonate 15α- and 15β-4-73:**



To a solution of diol **4-54** (15α/β 1:1.4, 270 mg, 0.528 mmol, R_f(hexane/ethyl acetate 2:1) = 0.4) in 7 mL of dry CH_2Cl_2 dry 2,6-lutidine (0.18 mL, 1.58 mmol, 3 equiv.) was added via syringe at –78 °C. After stirring the solution shortly, fresh triflic anhydride (0.091 mL, 0.55 mmol, 1.05 equiv.) was added very slowly under good stirring and the reaction mixture was stirred at –78 °C for ca. 30 min until complete by TLC (R_f of the sulfonylated alcohol (hexane/ethyl acetate 5:1) = 0.5). Subsequently triethylsilyl triflate (0.18 mL, 0.79 mmol, 1.5 equiv.) was added at –78 °C and the reaction was stirred at this temperature for another 30 min. The consumption was monitored by TLC (hexane/ethyl acetate 5:1 and 10:1). The reaction was quenched at –80 °C with 5 mL water, diluted with 20 mL diethyl ether and warmed to r.t. in 10 min. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed twice with $NaHCO_3$ solution, twice with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 400 mg of crude product. It was purified immediately on a short column (hexane/ethyl acetate 40:1, gradient to 20:1) to give 320 mg (81%) of **4-73** as an inseparable mixture of 15α/15β-isomers in a 1:1.2 ratio as a colourless oil, R_f (hexane/ethyl acetate 10:1) = 0.57, which was unstable and used immediately for the next step.

15α-/15β-**4-73:** IR (Film): $\tilde{\nu}$ = 2955 (m), 2932 (m), 2878 (w), 1464 (w), 1416 (m), 1377 (w), 1245 (m), 1207 (s), 1146 (m), 1068 (m), 1006 (m), 975 (w), 935 (s), 834 (s), 776 (s), 728 (s) cm^{-1}. - MS(ESI) *m/z* (%): 776 (16), 759 (48) [$M+H^+$], 758 (100) [M^+], 690 (8), 668 (13), 625 (28) [$M+Na^+$–TEMPO], 624 (57) [$M+Na^+$–TEMPOH], 608 (49) [M^+–TfOH], 557 (8), 536 (19), 535 (45), 494 (15) [M^+–OTf–TES], 476 (7) [$M+Na^+$–TEMPO–OTf], 379 (24) [M^+–TES–TBS–OTf] or [M^+–OTf–$CH_2CH(OTMP)C_5H_{11}$], 322 (8), 158 (16) [$TEMPOH_2^+$]. - HRMS: $C_{36}H_{70}F_3NO_6SSi_2^+$: calc. 758.4493; found 758.4495.

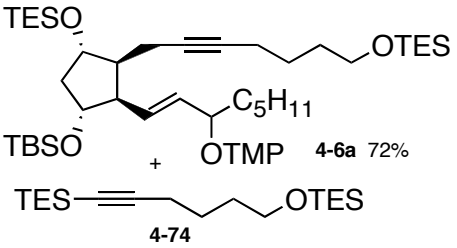
15β-**4-73**: ^{1}H NMR (400 MHz, C_6D_6): δ = –0.003 (s, 3H, Si(C*H*$_3$)$_2$), 0.000 (s, 3H, Si(C*H*$_3$)$_2$), 0.51 (q, *J* = 7.9 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.91 (t, *J* = 7.0 Hz, 3H, $CH_2CH_2CH_3$), 0.94 (s, 9H, SiC(C*H*$_3$)$_3$), 0.95 (t, *J* = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 1.09-1.21 (m, 13H, $NCCH_2CH_2CH_2CN$, NC(C*H*$_3$)$_2$), 1.24-1.40 (m, 8H, $NCCH_2CH_2CH_2CN$, $CH_2CH_2CH_2CH_2CH_3$), 1.40-1.61 (m, 4H,

TMPOCHCH_2, NCCH_2CH_2CH_2CN), 1.73 (m, 2H, CHCH_2CH, TMPOCHCH_2), 2.28 (dt, J = 13.9, 7.0 Hz, 1H, CHCH_2CH), 2.62 (dq, J = 8.1, 6.4 Hz, 1H, CHCH_2OSO$_2$CF$_3$), 2.82 (m, 1H, CHCHOTBS), 3.89 (dt, J = 6.5, 5.2 Hz, 1H, CHOTBS), 4.01 (dt, J = 7.3, 6.2 Hz, 1H, CHOTES), 4.17 (m, 1H, CHOTMP), 4.51 (A part of ABX system, J = 10.1, 6.1 Hz, 1H, CH_2OSO$_2$CF$_3$), 4.60 (B part of ABX system, J = 9.9, 6.4 Hz, 1H, CH_2OSO$_2$CF$_3$), 5.17 (dd, J = 15.3, 9.5 Hz, 1H, CH=CHCHOTMP), 5.54 (dd, J = 15.3, 8.6 Hz, 1H, =CHCHOTMP). - ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = –4.5 (q, Si(CH_3)$_2$), –4.4 (q, Si(CH_3)$_2$), 6.8 (t, SiCH$_2$), 7.1 (q, SiCH$_2$$CH_3$), 14.3 (q, CH$_2CH_2$$CH_3$), 17.7 (t, NCCH$_2$$CH_2CH_2$CN), 18.2 (s, Si$C$(CH$_3$)$_3$), 20.7 (q, NC($CH_3$)$_2$), 23.1 (t, CH$_2$$CH_2CH_3$), 25.7 (t, CH$_2CH_2CH_2CH_3$), 26.0 (q, SiC(CH$_3$)$_3$), 32.5 (t, CH$_2CH_2CH_3$), 34.6 (q, NC(CH$_3$)$_2$), 35.02 (t, TMPOCHCH$_2$), 35.05 (q, NC(CH$_3$)$_2$), 40.6 (t, NCCH$_2CH_2$$CH_2$CN), 44.8 (t, CH$CH_2$CH), 50.4 (d, CHCH$_2OSO_2CF_3$), 52.1 (d, CHCHOTBS), 59.4 (s, NC(CH$_3$)$_2$), 72.9 (d, CHOTES), 76.4 (d, CHOTBS), 77.3 (t, CH$_2$OTf), 84.9 (d, CHOTMP), 119.4 (q, $J_{C\text{-}F}$ = 320 Hz, CF$_3$), 128.5 (d, CH=CHCHOTMP), 138.0 (d, =CHCHOTMP).

15α-**4-73**: ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 0.02 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$), 0.52 (q, J = 7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.90 (t, J = 8.1 Hz, 9H, Si(CH$_2$CH_3)$_3$), 0.91 (t, J = 7.0 Hz, 3H, CH$_2$CH$_2$CH_3), 0.93 (s, 9H, SiC(CH_3)$_3$), 1.09-1.21 (m, 13H, NCCH$_2$CH_2CH$_2$CN, NC(CH_3)$_2$), 1.24-1.40 (m, 8H, NCCH_2CH$_2$CH$_2$CN, CH$_2$CH_2CH_2CH_2CH$_3$), 1.40-1.61 (m, 4H, TMPOCHCH_2, NCCH_2CH_2CH_2CN), 1.73 (m, 2H, CHCH_2CH, TMPOCHCH_2), 2.17 (ddd, J = 6.4, 7.8, 14.1 Hz, 1H, CHCH_2CH), 2.70 (quint, J = 7.1 Hz, 1H, CHCH_2OSO$_2$CF$_3$), 2.82 (m, 1H, CHCHOTBS), 3.91 (m, 1H, CHOTES), 3.96 (ddd, J = 13.7, 7.1, 3.3 Hz, 1H, CHOTBS), 4.17 (m, 1H, CHOTMP), 4.44 (m, 2H, CH_2OSO$_2$CF$_3$), 5.08 (dd, J = 15.3, 9.4 Hz, 1H, CH=CHCHOTMP), 5.53 (dd, J = 15.1, 8.7 Hz, 1H, =CHCHOTMP). - ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = –4.45 (q, Si(CH_3)$_2$), –4.41 (q, Si(CH_3)$_2$), 5.1 (t, SiCH$_2$), 7.0 (q, SiCH$_2$$CH_3$), 14.3 (q, CH$_2CH_2$$CH_3$), 17.7 (t, NCCH$_2$$CH_2CH_2$CN), 18.2 (s, Si$C$(CH$_3$)$_3$), 20.7 (q, NC($CH_3$)$_2$), 23.0 (t, CH$_2$$CH_2CH_3$), 25.7 (t, CH$_2CH_2CH_2CH_3$), 26.0 (q, SiC(CH$_3$)$_3$), 32.5 (t, CH$_2CH_2CH_3$), 34.6 (q, NC(CH$_3$)$_2$), 35.0 (t, TMPOCHCH$_2$), 35.3 (q, NC(CH$_3$)$_2$), 40.6 (t, NCCH$_2CH_2$$CH_2$CN), 44.6 (t, CH$CH_2$CH), 50.1 (d, CHCH$_2OSO_2CF_3$), 52.5 (d, CHCHOTBS), 60.5 (s, NC(CH$_3$)$_2$), 73.1 (d, CHOTES), 76.2 (d, CHOTBS), 77.1 (t, CH$_2$OTf), 85.2 (d, CHOTMP), 119.4 (q, $J_{C\text{-}F}$ = 320 Hz, CF$_3$), 127.5 (d, CH=CHCHOTMP), 138.1 (d, =CHCHOTMP).

6.9.5. Completion of the 20 carbon atom skeleton

(1*R,2*R**,3*S**,4*S**)-1-(*tert*-Butyldimethylsilyloxy)-3-[7-(triethylsilyloxy)hept-2-yn-1-yl]-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-4-(triethylsilyloxy)cyclopentane 15α- and 15β-4-6a:**



BuLi (0.21 mL, 0.336 mmol, 1.19 equiv. based on **4-9**, 1.6 *M* in hexane) was added to a solution of alkyne **4-9** (60 mg, 0.283 mmol, 1.95 equiv. based on **4-73**) in 4 mL THF/HMPA 5:1 and stirred at –60 - –40 °C for 25 min. Triflate **4-73** (110 mg, 0.145 mmol, 15β/α = 2.1:1) dissolved in 1 mL THF was added to the lithium acetylide at –78 °C. The vial and the syringe were rinsed with 1 mL THF and another 0.4 mL HMPA was added to the reaction mixture. The reaction mixture was stirred for 3 h from –78 to 0 °C, when finished by TLC (hexane/ethyl acetate 20:1). The reaction mixture was quenched with 10 mL water and diluted with diethyl ether at 0 °C. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum and the crude product was purified by flash column chromatography using a short column (hexane/ethyl acetate 5:1). Compounds **4-6a** (15β/α = 1.6:1), **4-9** and **4-74** were isolated as an inseparable mixture of 140 mg weight (R_f(hexane/ethyl acetate 20:1 = 0.4). The yield of 15α/β-**4-6a** was calculated to 72% from the ^{1}H NMR spectrum; that of **4-74** to 25%. The mixture was used without further separation in the next step.

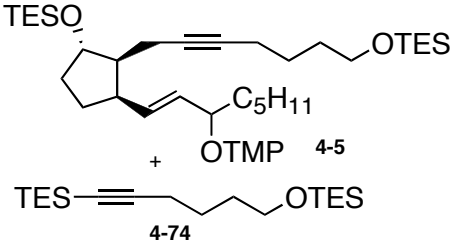
IR (Film): $\tilde{\nu}$ = 2953 (m), 2932 (m), 2876 (w), 1461 (w), 1377 (w), 1360 (w), 1251 (w), 1104 (m), 1006 (m), 974 (w), 835 (m), 775 (w), 725 (s), 670 (w) cm^{-1}. - MS(ESI) *m/z* (%): 820 (100) [M+H$^+$], 706 (22) [M+H$^+$–TBS], 688 (8) [M$^+$–TESOH], 608 (9), 494 (7), 158 [TEMPOH$_2^+$]. - HRMS: $C_{47}H_{94}NO_4Si_3^+$: calc. 820.6491; found 820.6504.

15β-**4-6a**: ^{1}H NMR (400 MHz, C_6D_6): δ = –0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.00 (s, 3H, Si(C*H*$_3$)$_2$), 0.39-0.60 (m, 12H, Si(C*H*$_2$CH$_3$)$_3$), 0.79-1.00 (m, 30H, SiC(C*H*$_3$)$_3$, Si(CH$_2$C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 1.02-1.30 (m, 19H, NCCH$_2$C*H*$_2$CH$_2$CN, NC(C*H*$_3$)$_2$, CH$_2$(C*H*$_2$)$_2$CH$_3$, (C*H*$_2$)$_2$CH$_2$OTES), 1.31-1.57 (m, 10H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, C*H*$_2$(CH$_2$)$_2$CH$_3$, C*H*$_2$CHOTMP, (C*H*$_2$)$_2$CH$_2$OTES), 1.74 (m, 2H, C*H*$_2$CHOTMP, CHC*H*$_2$CH), 2.02 (m, 4H, CHC*H*$_2$C≡, CH$_2$C*H*$_2$C≡), 2.20-2.48 (m, 2H, CHC*H*$_2$CH, C*H*CH$_2$C≡), 2.97 (m, 1H, C*H*CHOTBS), 3.45 (t, *J* = 5.7 Hz, 2H, C*H*$_2$OTES),

4.07 (m, 1H, C*H*OTBS), 4.17 (m, 2H, C*H*OTMP, C*H*OTES), 5.49 (m, 2H, C*H*=C*H*). - ^{13}C NMR (100 MHz, C_6D_6): δ = –4.3 (q, Si(*C*H$_3$)$_2$), –4.2 (q, Si(*C*H$_3$)$_2$), 5.1 (t, Si*C*H$_2$CH$_3$), 7.8 (q, SiCH$_2$*C*H$_3$), 14.4 (q, CH$_2$CH$_2$*C*H$_3$), 17.8 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.3 (s, Si*C*(CH$_3$)$_3$), 18.9 (t, CH$_2$*C*H$_2$C≡), 19.1 (t, CH*C*H$_2$C≡), 20.7 (q, NC(*C*H$_3$)$_2$), 20.8 (q, NC(*C*H$_3$)$_2$), 23.1 (t, CH$_2$*C*H$_2$CH$_3$), 25.6 (t, CH$_2$*C*H$_2$CH$_2$C≡), 26.08 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.15 (q, SiC(*C*H$_3$)$_3$), 32.2 (t, *C*H$_2$CH$_2$OTES), 32.6 (t, *C*H$_2$CH$_2$CH$_3$), 34.6 (q, NC(*C*H$_3$)$_2$), 35.20 (t, *C*H$_2$CHOTMP), 35.3 (q, NC(*C*H$_3$)$_2$), 40.7 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 45.2 (t, CH*C*H$_2$CH), 50.8 (d, *C*HCH$_2$C≡), 52.9 (d, CH*C*HCH=), 59.4 (s, N*C*(CH$_3$)$_2$), 60.4 (s, N*C*(CH$_3$)$_2$), 62.5 (t, *C*H$_2$OTES), 75.5 (d, *C*HOTES), 76.5 (d, *C*HOTBS), 80.1 (s, *C*≡C), 81.1 (s, *C*≡C), 85.4 (d, *C*HOTMP), 131.6 (d, *C*H=CHCHOTMP), 136.0 (d, =*C*HCHOTMP).

15α-**4-6a**: ^{1}H NMR (400 MHz, C_6D_6): δ = 0.01 (s, 3H, Si(C*H$_3$*)$_2$), 0.04 (s, 3H, Si(C*H$_3$*)$_2$), 0.39-0.60 (m, 12H, Si(C*H$_2$*CH$_3$)$_3$), 0.79-1.00 (m, 30H, SiC(C*H$_3$*)$_3$, Si(CH$_2$C*H$_3$*)$_3$, CH$_2$C*H$_3$*), 1.02-1.30 (m, 19H, NCCH$_2$C*H$_2$*CH$_2$CN, NC(C*H$_3$*)$_2$, CH$_2$(C*H$_2$*)$_2$CH$_3$, (C*H$_2$*)$_2$CH$_2$OTES), 1.31-1.57 (m, 10H, NCC*H$_2$*C*H$_2$*C*H$_2$*CN, C*H$_2$*(CH$_2$)$_2$CH$_3$, C*H$_2$*CHOTMP, (C*H$_2$*)$_2$CH$_2$OTES), 1.74 (m, 2H, C*H$_2$*CHOTMP, CHC*H$_2$*CH), 2.02 (m, 2H, CH$_2$C*H$_2$*C≡), 2.20-2.48 (m, 4H, CHC*H$_2$*CH, CHC*H$_2$*C≡, C*H*CH$_2$C≡), 2.97 (m, 1H, C*H*CHOTBS), 3.43 (t, *J* = 6.4 Hz, 2H, C*H$_2$*OTES), 3.96 (m, 1H, C*H*OTES), 4.07 (m, 1H, C*H*OTBS), 4.17 (m, 1H, C*H*OTMP), 5.30 (dd, *J* = 15.3, 9.2 Hz, 1H, C*H*=CHCHOTMP), 5.58 (m, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz, C_6D_6): δ = –4.3 (q, Si(*C*H$_3$)$_2$), –4.2 (q, Si(*C*H$_3$)$_2$), 5.3 (t, Si*C*H$_2$CH$_3$), 7.1 (q, SiCH$_2$*C*H$_3$), 14.4 (q, CH$_2$CH$_2$*C*H$_3$), 17.8 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.3 (s, Si*C*(CH$_3$)$_3$), 18.9 (t, CH$_2$*C*H$_2$C≡), 19.0 (t, CH*C*H$_2$C≡), 20.6 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 23.2 (t, CH$_2$*C*H$_2$CH$_3$), 25.79 (t, CH$_2$*C*H$_2$CH$_2$C≡), 25.84 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.2 (q, SiC(*C*H$_3$)$_3$), 32.3 (t, *C*H$_2$CH$_2$OTES), 32.5 (t, *C*H$_2$CH$_2$CH$_3$), 34.5 (q, NC(*C*H$_3$)$_2$), 35.16 (t, *C*H$_2$CHOTMP), 35.4 (q, NC(*C*H$_3$)$_2$), 40.8 (t, NC*C*H$_2$CH$_2$*C*H$_2$CN), 45.1 (t, CH*C*H$_2$CH), 50.6 (d, *C*HCH$_2$C≡), 53.4 (d, CH*C*HCH=), 59.4 (s, N*C*(CH$_3$)$_2$), 60.5 (s, N*C*(CH$_3$)$_2$), 62.5 (t, *C*H$_2$OTES), 75.9 (d, *C*HOTES), 76.1 (d, *C*HOTBS), 79.7 (s, *C*≡C), 80.8 (s, *C*≡C), 85.8 (d, *C*HOTMP), 129.8 (d, *C*H=CHCHOTMP), 136.3 (d, =*C*HCHOTMP).

(1*S,2*S**,3*R**)-2-[7-(triethylsilyloxy)hept-2-yn-1-yl]-3-[(*R**,*E* *and* *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-1-(triethylsilyloxy)cyclopentane 15α- and 15β-4-5:**

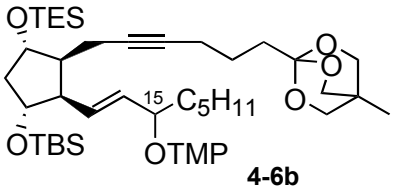


The alkylation of a mixture of 15α–**4–71**/15β–**4–71**/**4-71TES$_2$** (5:1:2, 120 mg), containing 91 mg (0.14 mmol) of triflates **4-71** and 29 mg (0.047 mmol) of **4-71TES$_2$**, with alkyne **4-9** (111 mg, 0.52 mmol) was performed similar to the alkylation of compound **4-73**, with the exception that the reaction time was much longer (5.5 h at –78 - –10 °C, then 17 h at –10 °C - r.t.). The prolonged reaction time was probably the reason for low yields. Purification of the crude product by flash column chromatography with hexane/ethyl acetate 20:1 gradient to 10:1 afforded compounds 15β/α-**4-5**, **4-9**, **4-74** and **4-71TES$_2$** as an inseparable mixture of 110 mg weight (R_f(hexane/ethyl acetate 20:1 = 0.37-0.49). After a second purification, two fractions of 40 mg and 20 mg, both containing the same mixture in different ratios were isolated. The yield of 15α/β-**4-5** was calculated to 29% (27.9 mg) from the ^{1}H NMR spectrum; that of **4-74** to 6% (11.8 mg).

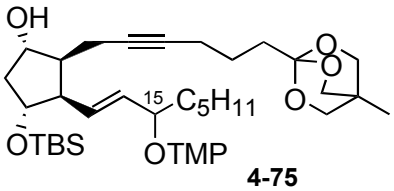
15α-**4-5**: ^{1}H NMR (400 MHz, C_6D_6): δ = 0.62 (m, 12H, Si(C*H*$_2$CH$_3$)$_3$), 0.88-1.13 (m, 21H, Si(CH$_2$C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 1.14-1.42 (m, 18H, NCCH$_2$C*H*$_2$CH$_2$CN, NC(C*H*$_3$)$_2$, CH$_2$(C*H*$_2$)$_2$CH$_3$), 1.43-1.71 (m, 14H, NCC*H*$_2$CH$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$, (C*H*$_2$)$_2$CH$_2$OTES, (C*H*$_2$)$_2$CHOTES), 1.79-1.96 (m, 2H, C*H*$_2$CHOTMP, C*H*$_2$CHOTES), 2.14-2.41 (m, 5H, C*H*C*H*$_2$C≡, CH$_2$C*H*$_2$C≡), 3.13 (m, 1H, C*H*CH=CHCHOTMP), 3.57 (t, *J* = 6.0 Hz, 2H, C*H*$_2$OTES), 4.26 (m, 2H, C*H*OTMP, C*H*OTES), 5.55 (m, 2H, C*H*=C*H*). - ^{13}C NMR (100 MHz, C_6D_6): δ = 5.1 (t, SiC*H*$_2$CH$_3$), 7.8 (q, SiCH$_2$C*H*$_3$), 14.3 (q, CH$_2$CH$_2$C*H*$_3$), 17.8 (t, NCCH$_2$C*H*$_2$CH$_2$CN), 18.5 (t, CH$_2$C*H*$_2$C≡), 19.1 (t, CHC*H*$_2$C≡), 20.6 (q, NC(C*H*$_3$)$_2$), 20.8 (q, NC(C*H*$_3$)$_2$), 23.1 (t, CH$_2$C*H*$_2$CH$_3$), 25.8 (t, C*H*$_2$CH$_2$CH$_2$CH$_3$), 26.1 (t, CH$_2$C*H*$_2$CH$_2$C≡), 27.9 (t, C*H*$_2$CH$_2$CHOTES), 32.4 (t, C*H*$_2$CH$_2$OTES), 32.5 (t, C*H*$_2$CH$_2$CH$_3$), 34.5 (q+t, NC(C*H*$_3$)$_2$, C*H*$_2$CHOTES), 35.1 (t, C*H*$_2$CHOTMP), 35.9 (q, NC(C*H*$_3$)$_2$), 40.7 (t, NCC*H*$_2$CH$_2$C*H*$_2$CN), 43.2 (d, C*H*CH=CHCHOTMP), 52.9 (d, C*H*CH$_2$C≡), 59.2 (s, NC(CH$_3$)$_2$), 60.5 (s, NC(CH$_3$)$_2$), 62.5 (t, C*H*$_2$OTES), 77.5 (d, C*H*OTES), 79.8 (s, C≡C), 80.8 (s, C≡C), 85.9 (d, C*H*OTMP), 132.9 (d, C*H*=CHCHOTMP), 134.4 (d, =C*H*CHOTMP).

15β-**4-5** (detectable resonances): ^{1}H NMR (400 MHz, C_6D_6): δ = 0.62 (m, 12H, Si(C*H*$_2$CH$_3$)$_3$), 0.88-1.13 (m, 21H, Si(CH$_2$C*H*$_3$)$_3$, CH$_2$C*H*$_3$), 1.14-1.42 (m, 18H, NCCH$_2$C*H*$_2$CH$_2$CN, NC(C*H*$_3$)$_2$, CH$_2$(C*H*$_2$)$_2$CH$_3$), 1.43-1.71 (m, 14H, NCC*H*$_2$CH$_2$C*H*$_2$CN, C*H*$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$, (C*H*$_2$)$_2$CH$_2$OTES, (C*H*$_2$)$_2$CHOTES), 1.79-1.96 (m, 2H, C*H*$_2$CHOTMP, C*H*$_2$CHOTES), 2.14-2.41 (m, 5H, C*H*C*H*$_2$C≡, CH$_2$C*H*$_2$C≡), 3.13 (m, 1H, C*H*CH=CHCHOTMP), 3.57 (t, *J* = 6.0 Hz, 2H, C*H*$_2$OTES), 4.26 (m, 2H, C*H*OTMP, C*H*OTES), 5.51 (m, 1H, C*H*=CHCHOTMP), 5.63 (dd, *J* = 15.5, 7.6 Hz, 1H, C*H*CHOTMP). - ^{13}C NMR (100 MHz, C_6D_6): δ = 52.8 (d, *C*HCH$_2$C≡), 62.5 (t, *C*H$_2$OTES), 76.1 (d, *C*HOTES), 85.6 (d, *C*HOTMP), 133.7 (d, *C*H=CHCHOTMP), 135.1 (d, =*C*HCHOTMP).

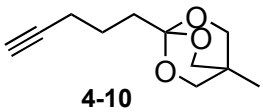
(1*R,2*R**,3*S**,4*S**)-1-(*tert*-Butyldimethylsilyloxy)-3-[6-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-yn-1-yl]-2-[(*R*,E* and *S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-4-(triethylsilyloxy)cyclopentane 15α- and 15β-4-6b and corresponding deprotected alcohols 15α- and 15β-4-75b:**



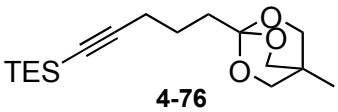
4-6b



4-75



4-10



4-76

4-Methyl-1-(4-pentynyl)-2,6,7-trioxabicyclo[2.2.2]octane **4-10** (59 mg, 0.3 mmol, 3 equiv. based on triflate **4-73**) dissolved in 3 mL dry THF and 1 mL dry HMPA was treated with BuLi (0.225 mL, 0.36 mmol, 1.6*M* in hexane, 1.2 equiv. based on **4-10**) at –78 - –45 °C for 35 min. Triflate **4-73** (15α/β 1:1.2, 80 mg, 0.1 mmol) dissolved in 1 mL dry THF was added to the lithium acetylide solution at –78 °C. The vial and the syringe were rinsed twice with 0.5 mL THF. The reaction mixture was stirred from –78 to –15 °C for 2 h and 10 min, and another 30 min at –15 °C until complete by TLC (hexane/ethyl acetate 5:1 and 10:1). The reaction mixture was quenched with 10 mL water and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum and the crude product (440 mg) was purified on a short column (hexane/ethyl acetate/triethylamine 40:1:1 gradient 30:1:1 and 10:5:1). The products eluted in the following order: 40 mg (50 %) **4-6b** as an inseparable mixture of 15α/15β-isomers in a 1:1.6 ratio, R_f(hexane/ethyl acetate 5:1) = 0.6; 27 mg (29%)

of 4-methyl-1-(5-triethylsilyl-4-pentynyl)-2,6,7-trioxabicyclo[2.2.2]octane **4-76**, R_f(hexane/ethyl acetate 5:1) = 0.5; 16 mg (10%) of alkyne **4-10**, R_f(hexane/ethyl acetate 5:1) = 0.38; 24 mg of **4-75** as an inseparable mixture of 15α/15β-isomers in a 1:1.2 ratio, R_f(hexane/ethyl acetate 2:1) = 0.62. Because of co-migration with NEt_3, product **4-75** cannot be detected on TLC. It was isolated by collecting all fractions eluting with hexane/ethyl acetate/NEt_3 10:5:1. Further purification of these 24 mg gave 18 mg (26%) of **4-75**.

15α-/15β-**4-6b:** IR (Film): $\tilde{\nu}$ = 2954 cm^{-1} (s), 2931 (s), 2875 (m), 1462 (w), 1397 (w), 1377 (w), 1358 (w), 1253 (w), 1186 (w), 1062 (s), 1005 (m), 959 (m), 891 (w), 836 (s), 776 (m), 744 (m), 727 (m), 669 (w). - MS(ESI) *m/z* (%): 804 (100) [$M+H^+$]. - HRMS: $C_{46}H_{86}NO_6Si_2^+$: calc. 804.5994; found 804.6012.

15β-**4-6b**: ^{1}H NMR (400 MHz, C_6D_6): δ = –0.10 (s, 3H, $(OCH_2)_3CCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.46-0.62 (m, 6H, $Si(CH_2CH_3)_3$), 0.80 (m, 3H, $CH_2CH_2CH_3$), 0.84-1.03 (m, 18H, $SiC(CH_3)_3$, $Si(CH_2CH_3)_3$), 1.07-1.42 (m, 24H, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$, $CH_2(CH_2)_3CH_3$), 1.51 (m, 1H, $CH_2CHOTMP$), 1.70 (m, 2H, $CH_2CHOTMP$, $CHCH_2CH$), 1.84 (m, 2H, $CH_2CH_2C(OCH_2)_3$), 1.97 (m, 2H, $CH_2C(OCH_2)_3$), 2.05 (m, 2H, $\equiv CCH_2CH_2$), 2.18 (m, 2H, $CHCH_2C\equiv$), 2.29 (m, 1H, $CHCH_2CH$), 2.42 (m, 1H, $CHCH_2C\equiv$), 2.99 (m, 1H, CHCHOTBS), 3.42 (s, 6H, $CH_2C(OCH_2)_3$), 4.05 (m, 1H, CHOTBS), 4.18 (m, 2H, CHOTES, CHOTMP), 5.50 (m, 2H, CH=CH). - ^{13}C NMR (100 MHz): δ = –4.3 (q, $SiCH_3$), –4.2 (q, $SiCH_3$), 5.4 (t, $SiCH_2CH_3$), 7.2 (q, $SiCH_2CH_3$), 14.0 (q, $(OCH_2)_3CCH_3$), 14.4 (q, $CH_2CH_2CH_3$), 17.8 (t, $NCCH_2CH_2$), 18.3 (s, $SiC(CH_3)_3$), 19.1 (t, $CHCH_2C\equiv$), 19.2 (t, $CH_2CH_2C\equiv$), 20.8 (q, $NC(CH_3)_2$), 23.1 (t, $CH_2CH_2CH_3$), 23.7 (t, $CH_2CH_2C\equiv$), 25.8 (t, $CH_2CH_2CH_2CH_3$), 26.2 (q, $SiC(CH_3)_3$), 29.9 (s, $(OCH_2)_3CCH_3$), 32.6 (t, $CH_2CH_2CH_3$), 34.6 (q, $NC(CH_3)_2$), 35.2 (t, $CH_2CHOTMP$), 35.9 (q, $NC(CH_3)_2$), 36.6 (t, $CH_2C(OCH_2)_3$), 40.7 (t, $NCCH_2CH_2$), 45.2 (t, $CHCH_2CH$), 50.9 (d, $CHCH_2C\equiv$), 53.0 (d, CHCHCH=), 60.5 (s, $NC(CH_3)_2$), 72.5 (t, $CH_2C(OCH_2)_3$), 75.5 (d, CHOTES), 76.6 (d, CHOTBS), 80.1 (s, C≡C), 81.4 (s, C≡C), 85.3 (d, CHOTMP), 109.5 (s, $CH_2C(OCH_2)_3$), 131.9 (d, CH=CHCHOTMP), 136.0 (d, =CHCHOTMP).

15α-**4-6b**: ^{1}H NMR (400 MHz, C_6D_6): δ = –0.09 (s, 3H, $(OCH_2)_3CCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.46-0.62 (m, 6H, $Si(CH_2CH_3)_3$), 0.80 (m, 3H, $CH_2CH_2CH_3$), 0.84-1.03 (m, 18H, $SiC(CH_3)_3$, $Si(CH_2CH_3)_3$), 1.07-1.42 (m, 24H, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$, $CH_2(CH_2)_3CH_3$), 1.51 (m, 1H, $CH_2CHOTMP$), 1.70 (m, 2H, $CH_2CHOTMP$, $CHCH_2CH$), 1.84 (m, 2H, $CH_2CH_2C(OCH_2)_3$), 1.97 (m, 2H, $CH_2C(OCH_2)_3$), 2.05 (m, 2H, $\equiv CCH_2CH_2$), 2.18 (m, 2H, $CHCH_2C\equiv$), 2.29 (m, 1H, $CHCH_2CH$), 2.42 (m, 1H, $CHCH_2C\equiv$), 2.99 (m, 1H,

C*H*CHOTBS), 3.44 (s, 6H, $CH_2C(OCH_2)_3$), 3.99 (m, 1H, C*H*OTES), 4.05 (m, 1H, C*H*OTBS), 4.18 (m, 1H, C*H*OTMP), 5.33 (dd, *J* = 15.4, 9.2 Hz, 1H, C*H*=CHCHOTMP), 5.64 (dd, *J* = 15.4, 8.6 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = –4.3 (q, Si*C*H_3), –4.17 (q, Si*C*H_3), 5.3 (t, Si*C*H_2CH_3), 7.1 (q, $SiCH_2CH_3$), 14.0 (q, $(OCH_2)_3CCH_3$), 14.4 (q, $CH_2CH_2CH_3$), 17.8 (t, $NCCH_2CH_2$), 18.3 (s, Si*C*$(CH_3)_3$), 19.0 (t, $CHCH_2C{\equiv}$), 19.2 (t, $CH_2CH_2C{\equiv}$), 20.6 (q, $NC(CH_3)_2$), 23.2 (t, $CH_2CH_2CH_3$), 23.7 (t, $CH_2CH_2C{\equiv}$), 25.8 (t, $CH_2CH_2CH_2CH_3$), 26.24 (q, $SiC(CH_3)_3$), 29.9 (s, $(OCH_2)_3CCH_3$), 32.5 (t, $CH_2CH_2CH_3$), 34.5 (q, $NC(CH_3)_2$), 35.0 (t, $CH_2CHOTMP$), 35.9 (q, $NC(CH_3)_2$), 36.5 (t, $CH_2C(OCH_2)_3$), 40.5 (t, $NCCH_2CH_2$), 40.8 (t, $NCCH_2CH_2$), 45.1 (t, $CHCH_2CH$), 50.6 (d, $CHCH_2C{\equiv}$), 53.5 (d, CHCHCH=), 59.4 (s, $NC(CH_3)_2$), 72.5 (t, $CH_2C(OCH_2)_3$), 75.8 (d, *C*HOTES), 76.3 (d, *C*HOTBS), 79.7 (s, *C*≡C), 81.0 (s, *C*≡C), 85.9 (d, *C*HOTMP), 109.5 (s, $CH_2C(OCH_2)_3$), 129.9 (d, *C*H=CHCHOTMP), 136.3 (d, =*C*HCHOTMP).

(*1S*,2S*,3R*,4R)-4-(*tert*-Butyldimethylsilyloxy)-2-[6-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-yn-1-yl]-3-[(*R*,E* and *S*,E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentanol 4-75:**

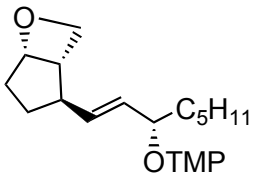
15α-/15β-**4-75**: IR (Film): $\tilde{\nu}$ = 3436 cm^{-1} (br. w), 2929 (s), 2874 (m), 1464 (w), 1398 (w), 1378 (w), 1356 (w), 1261 (m), 1188 (w), 1132 (w), 1058 (s), 993 (s), 959 (s), 889 (w), 837 (m), 777 (m). - MS(ESI) *m/z* (%): 713 (22) [M+Na^+ with ^{13}C], 712 (46) [M+Na^+], 691 (48) [M+H^+ with ^{13}C], 690 (100) [M+H^+], 305 (26), 158 (17) [$TEMPOH_2^+$]. - HRMS: $C_{40}H_{72}NO_6Si^+$: calc. 690.5129; found 690.5133.

15β-**4-75**: ^{1}H NMR (600 MHz, C_6D_6): δ = –0.14 (s, 3H, $(OCH_2)_3CCH_3$), 0.00 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3), 0.84 (m, 3H, CH_2CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.05-1.46 (m, 24H, $NC(CH_3)_2$, $NCCH_2CH_2CH_2CN$, $CH_2(CH_2)_3CH_3$), 1.50 (m, 1H, $CH_2CHOTMP$), 1.63 (m, 1H, $CHCH_2CH$), 1.77 (m, 1H, $CH_2CHOTMP$), 1.82 (m, 2H, $CH_2CH_2C(OCH_2)_3$), 2.01 (m, 4H, $\equiv CCH_2CH_2CH_2C(OCH_2)_3$), 2.05 (m, 2H, $CHCH_2C{\equiv}$), 2.12 (m, 1H, $CHCH_2CH$), 2.41 (m, 1H, $CHCH_2C{\equiv}$), 2.79 (m, 1H, TBSOCHC*H*), 3.41 (s, 6H, $CH_2C(OCH_2)_3$), 3.88 (m, 1H, C*H*OTBS), 3.95 (m, 1H, C*H*OH), 4.09 (m, 1H, C*H*OTMP), 5.05 (dd, *J* = 15.2, 9.8 Hz, 1H, C*H*=CHCHOTMP), 5.47 (dd, *J* = 15.3, 8.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz): δ = –4.45 (q, Si*C*H_3), –4.35 (q, Si*C*H_3), 13.91 (q, $(OCH_2)_3CCH_3$), 14.4 (q, CH_2CH_3), 17.7 (t, $NCCH_2CH_2$), 18.3 (s, Si*C*$(CH_3)_3$), 18.8 (t, $CH_2CH_2C{\equiv}$), 19.6 (t, $CHCH_2C{\equiv}$), 20.5 (q, $NC(CH_3)_2$), 20.8 (q, $NC(CH_3)_2$), 23.2 (t, CH_2CH_3), 23.6 (t, $CH_2CH_2C{\equiv}$), 25.8 (t, $CH_2CH_2CH_2CH_3$), 26.2 (q, $SiC(CH_3)_3$), 29.84 (s, $(OCH_2)_3CCH_3$), 32.43 (t, $CH_2CH_2CH_3$), 34.4 (q, $NC(CH_3)_2$), 35.0 (t, $CH_2CHOTMP$), 35.9 (q, $NC(CH_3)_2$), 36.2 (t, $CH_2C(OCH_2)_3$),

40.56 (t, NC*C*H$_2$CH$_2$), 40.59 (t, NC*C*H$_2$CH$_2$), 43.9 (t, CH*C*H$_2$CH), 50.32 (d, *C*HCH$_2$C≡), 54.8 (d, CH*C*HCH=), 59.3 (s, N*C*(CH$_3$)$_2$), 60.4 (s, N*C*(CH$_3$)$_2$), 72.40 (t, CH$_2$C(O*C*H$_2$)$_3$), 76.5 (d, *C*HOTBS), 77.0 (d, *C*HOH), 79.9 (s, *C*≡C), 81.3 (s, *C*≡C), 85.8 (d, *C*HOTMP), 109.5 (s, CH$_2$*C*(OCH$_2$)$_3$), 129.6 (d, *C*H=CHCHOTMP), 136.5 (d, =*C*HCHOTMP).

15α-**4-75**: ^{1}H NMR (600 MHz, C_6D_6): δ = –0.12 (d, *J* = 1.1 Hz, 3H, (OCH$_2$)$_3$CC*H$_3$*), –0.03 (s, 3H, SiC*H$_3$*), –0.02 (s, 3H, SiC*H$_3$*), 0.84 (m, 3H, CH$_2$C*H$_3$*), 0.87 (s, 9H, SiC(C*H$_3$*)$_3$), 1.05-1.46 (m, 24H, NC(C*H$_3$*)$_2$, NCC*H$_2$*C*H$_2$*C*H$_2$*CN, CH$_2$(C*H$_2$*)$_3$CH$_3$), 1.50 (m, 1H, C*H$_2$*CHOTMP), 1.71 (m, 1H, CHC*H$_2$*CH), 1.77 (m, 1H, C*H$_2$*CHOTMP), 1.87 (m, 2H, C*H$_2$*CH$_2$C(OCH$_2$)$_3$), 2.01 (m, 4H, ≡CC*H$_2$*CH$_2$C*H$_2$*C(OCH$_2$)$_3$), 2.05 (m, 2H, CHC*H$_2$*C≡), 2.25 (m, 1H, CHC*H$_2$*CH), 2.35 (m, 1H, C*H*CH$_2$C≡), 2.79 (m, 1H, TBSOCHC*H*), 3.41 (d, *J* = 1.8 Hz, 6H, CH$_2$C(OC*H$_2$*)$_3$), 3.88 (m, 1H, C*H*OH), 4.03 (m, 1H, C*H*OTBS), 4.14 (m, 1H, C*H*OTMP), 5.22 (dd, *J* = 15.3, 9.6 Hz, 1H, C*H*=CHCHOTMP), 5.43 (dd, *J* = 15.3, 8.9 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz): δ = –4.43 (q, Si*C*H$_3$), –4.41 (q, Si*C*H$_3$), 13.93 (q, (OCH$_2$)$_3$C*C*H$_3$), 14.4 (q, CH$_2$*C*H$_3$), 17.7 (t, NCCH$_2$*C*H$_2$), 18.3 (s, Si*C*(CH$_3$)$_3$), 18.9 (t, CH$_2$*C*H$_2$C≡), 19.7 (t, CH*C*H$_2$C≡), 20.5 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 23.1 (t, *C*H$_2$CH$_3$), 23.4 (t, *C*H$_2$CH$_2$C≡), 25.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.1 (q, SiC(*C*H$_3$)$_3$), 29.86 (s, (OCH$_2$)$_3$*C*CH$_3$), 32.47 (t, *C*H$_2$CH$_2$CH$_3$), 34.6 (q, NC(*C*H$_3$)$_2$), 35.1 (t, *C*H$_2$CHOTMP), 35.2 (q, NC(*C*H$_3$)$_2$), 36.3 (t, *C*H$_2$C(OCH$_2$)$_3$), 40.47 (t, NC*C*H$_2$CH$_2$), 40.7 (t, NC*C*H$_2$CH$_2$), 44.0 (t, CH*C*H$_2$CH), 50.26 (d, *C*HCH$_2$C≡), 54.2 (d, CH*C*HCH=), 59.3 (s, N*C*(CH$_3$)$_2$), 60.5 (s, N*C*(CH$_3$)$_2$), 72.41 (t, CH$_2$C(O*C*H$_2$)$_3$), 76.2 (d, *C*HOTBS), 77.1 (d, *C*HOH), 80.2 (s, *C*≡C), 81.6 (s, *C*≡C), 85.2 (d, *C*HOTMP), 109.5 (s, CH$_2$*C*(OCH$_2$)$_3$), 131.4 (d, *C*H=CHCHOTMP), 135.9 (d, =*C*HCHOTMP).

(*1S*,2S*,5R)-5-[(*1E,3S**)-3-(2,2,6,6-Tetramethylpiperidin-1-yloxy)oct-1-en-yl]-2-oxabicyclo[3.2.0]heptane 15α-4-81:**



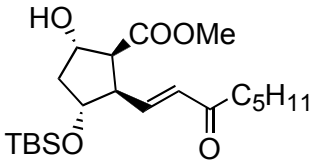
6-Hexynoic acid **4-77** (23 mg, 0.2 mmol, 3 equiv. based on bromide **4-65**) dissolved in 3 mL dry THF and 1 mL dry HMPA was treated with BuLi (0.26 mL, 1.6*M* in hexan, 0.41 mmol, 2.1 equiv. based on **4-77**) at –78 - –45 °C for 35 min. Bromide 15α/β-**4-65** 2.7:1 (30 mg, 0.067 mmol) dissolved in 1 mL dry THF was added to the lithium acetylide solution at –78 °C. The reaction mixture was stirred from –78 to –15 °C for 2 h when it was complete as indicated by TLC (hexane/ethyl acetate 5:1). The reaction was quenched with 10 mL of a

0.1*M* H_2SO_4 solution and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was evaporated in vacuum and the crude product was purified by flash chromatography with hexane/ethyl acetate 20:1, gradient to 2:1 to give the product **4-81** as a predominant 15α-isomer, R_f(hexane/ethyl acetate 5:1) = 0.54. 15β-**4-81** was detected in trace amounts. Yield: 20 mg as a colourless oil (82%).

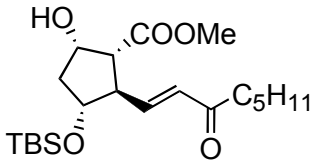
15α-**4-81**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.5 Hz, 3H, $CH_2CH_2CH_3$), 1.03-1.90 (m, 30H, $OCHCH_2CH_2$, $NC(CH_3)_2$, $NCCH_2CH_2CH_2CN$, $(CH_2)_4CH_3$), 2.48 (m, 1H, $CHCH_2OCH$), 2.66 (m, 1H, CH_2CHCH=), 3.12 (m, 1H, $CHOCH_2$), 3.94 (m, 1H, CHOTMP), 4.13 (A part of ABX, *J* = 6.2, 4.6 Hz, 1H, CH_2OCH), 4.78 (B part of ABX, *J* = 7.7, 6.3 Hz, 1H, CH_2OCH), 5.29 (m, 2H, CH=CH). - ^{13}C NMR (50 MHz): δ = 14.0 (q, CH_2CH_3), 17.3 (t, $NCCH_2CH_2CH_2CN$), 20.0 (q, $NC(CH_3)_2$), 20.1 (q, $NC(CH_3)_2$), 22.6 (t, CH_2CH_3), 25.1 (t, $CH_2CH_2CH_2CH_3$), 29.6 (t, $CH_2CH_2CHOCH_2$), 31.8 (t, $CH_2CH_2CH_3$), 32.8 (t, CH_2CHOCH_2), 33.0 (q, $NC(CH_3)_2$), 34.5 (t, $CH_2CHOTMP$), 35.1 (q, $NC(CH_3)_2$), 40.2 (t, $NCCH_2CH_2CH_2CN$), 43.4 (d, CH_2CHCH=), 45.0 (d, $CHCH_2O$), 74.4 (t, CH_2OCH), 85.2 (d, CHOTMP), 88.4 (d, $CHOCH_2$), 131.9 (d, CH=), 133.6 (d, =CHCHOTMP).
15β-**4-81** (detectable resonances): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.20 (m, 1H, CH=).

6.9.6. Completion of the total synthesis of 15-F_{2t}-IsoP

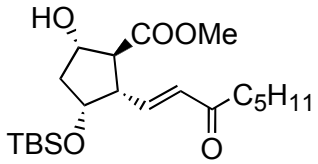
Methyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*E*)-3-oxo-oct-1-en-1-yl]cyclopentanecarboxylates:



4-83



4-84



4-85 = 12-*epi*-**4-83**

*m*CPBA (70%, 48 mg, 0.195 mmol, 1.5 equiv.) was added to a solution of 70 mg (0.13 mmol) of methyl esters 15α,β-**4-8a** and 15α,β-**4-50a** (IsoP:PG:3rd isomer 13:8:1) in 4 mL dry CH_2Cl_2 at 0 °C. The reaction was monitored by TLC (hexane/ethyl acetate 2:1: R_f(**4-83a**) = 0.39, R_f(**4-84a**) = 0.48, R_f(substrate) = 0.62 and R_f(*m*CPBA) = 0.69). After 30 min, the reaction mixture was quenched with 5 mL concentrated $Na_2S_2O_3$ solution, diluted with ethyl acetate and stirred at r.t. for 10 min. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and

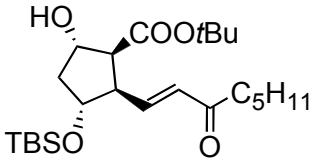
concentrated in vacuum. The crude product was purified on a short column with hexane/ethyl acetate 20:1, gradient to 2:1. The products were isolated as an inseparable mixture of **4-83a**, **4-84a** and **4-85a** in a ratio 4.3:4.5:1. Yield: 38 mg (73%). Identical experiments were performed with *t*Bu-esters **4-8b** and **4-50b**. Flash chromatography afforded **4-84b**, followed by a mixture of **4-83b**, **4-85b** and **4-86b**. For yields and ratios see Table 4.24.

4-84a: ^{1}H NMR (400 MHz): δ = –0.007 or 0.000 (s, 3H, Si(C*H*$_3$)$_2$), 0.000 or 0.006 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (m, 3H, CH$_2$C*H*$_3$), 0.824 (s, 9H, SiC(C*H*$_3$)$_3$), 1.24 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.54 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.85 (dt, *J* = 14.1, 2.4 Hz, 1H, C*H*$_2$CHOH), 2.08 (ddd, *J* = 14.1, 6.1, 5.3 Hz, 1H, C*H*$_2$CHOH), 2.43 or 2.45 (t, *J* = 7.6 Hz, 2H, C*H*$_2$CO), 2.67 (dd, *J* = 9.5, 5.3 Hz, 1H, C*H*COOMe), 3.27 (dt, *J* = 4.3, 9.0 Hz, 1H, C*H*CH=CH), 3.59 or 3.68 (s, 3H, COOC*H*$_3$), 4.04 (m, 1H, C*H*OTBS), 4.44 (m, 1H, C*H*OH), 6.13 (dd, *J* = 15.7, 0.9 Hz, 1H, =C*H*CO), 6.59 (dd, *J* = 15.7, 8.7 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = –4.92 or –4.89 (q, Si(*C*H$_3$)$_2$), –4.86 or –4.82 (q, Si(*C*H$_3$)$_2$), 13.8 (q, CH$_2$*C*H$_3$), 17.8 (s, Si*C*(CH$_3$)$_3$), 22.3 (t, *C*H$_2$CH$_3$), 23.7 or 23.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.60 or 25.63 (q, SiC(*C*H$_3$)$_3$), 31.32 or 31.34 (t, *C*H$_2$CH$_2$CH$_3$), 40.2 or 40.9 (t, CH$_2$*C*H$_2$CO), 43.2 (t, CH*C*H$_2$CH), 51.6 (d, CH*C*HCH=), 51.7 or 52.0 (q, O*C*H$_3$), 55.2 (d, *C*HCOOMe), 73.8 (d, *C*HOH), 77.9 (d, *C*HOTBS), 130.3 (d, =*C*HCO), 145.0 (d, *C*H=CHCO), 171.6 or 172.8 (s, *C*OOMe), 200.10 or 200.14 (s, C=O).

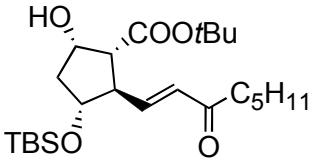
4-83a: ^{1}H NMR (400 MHz): δ = –0.007 or 0.000 (s, 3H, Si(C*H*$_3$)$_2$), 0.000 or 0.006 (s, 3H, Si(C*H*$_3$)$_2$), 0.80 (m, 3H, CH$_2$C*H*$_3$), 0.821 (s, 9H, SiC(C*H*$_3$)$_3$), 1.24 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.54 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.72 (dt, *J* = 14.0, 4.0 Hz, 1H, C*H*$_2$CHOH), 2.37 (ddd, *J* = 14.1, 7.1, 5.8 Hz, 1H, C*H*$_2$CHOH), 2.43 or 2.45 (t, *J* = 7.6 Hz, 2H, C*H*$_2$CO), 3.06 (m, 1H, C*H*CH=CH), 3.20 (dd, *J* = 8.6, 4.6 Hz, 1H, C*H*COOMe), 3.59 or 3.68 (s, 3H, COOC*H*$_3$), 4.11 (m, 1H, C*H*OTBS), 4.50 (m, 1H, C*H*OH), 6.05 (dd, *J* = 15.7, 0.4 Hz, 1H, =C*H*CO), 6.43 (dd, *J* = 15.8, 9.7 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = –4.92 or –4.89 (q, Si(*C*H$_3$)$_2$), –4.86 or –4.82 (q, Si(*C*H$_3$)$_2$), 13.8 (q, CH$_2$*C*H$_3$), 17.70 or 17.83 (s, Si*C*(CH$_3$)$_3$), 22.3 (t, *C*H$_2$CH$_3$), 23.7 or 23.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.60 or 25.63 (q, SiC(*C*H$_3$)$_3$), 31.32 or 31.34 (t, *C*H$_2$CH$_2$CH$_3$), 40.2 or 40.9 (t, CH$_2$*C*H$_2$CO), 42.8 (t, CH*C*H$_2$CH), 51.7 or 52.0 (q, O*C*H$_3$), 53.1 (d, CH*C*HCH=), 56.2 (d, *C*HCOOMe), 73.5 (d, *C*HOH), 76.9 (d, *C*HOTBS), 132.0 (d, =*C*HCO), 142.5 (d, *C*H=CHCO), 171.6 or 172.8 (s, *C*OOMe), 200.10 or 200.14 (s, C=O).

4-85a (detectable resonances): ^{1}H NMR (400 MHz): δ = 2.08 (m, 1H, C*H*$_2$CHOH), 2.19 (m, 1H, C*H*$_2$CHOH), 2.80 (m, 1H, C*H*CH=CH), 2.98 (dd, *J* = 9.8, 3.4 Hz, 1H, C*H*COOMe), 3.65 (s, 3H, COOC*H*$_3$), 4.29 (br. t, *J* = 3.6 Hz, 1H, C*H*OTBS), 4.36 (m, 1H, C*H*OH), 6.07 (dd, *J* = 16.0, 0.7 Hz, 1H, =C*H*CO), 6.82 (dd, *J* = 16.0, 8.5 Hz, 1H, C*H*=CHCO).

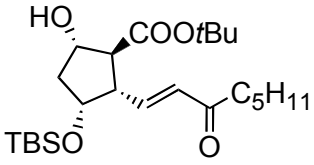
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2-[(*E)*-3-oxo-oct-1-en-1-yl]cyclopentanecarboxylates:**



4-83b



4-84b



4-85b

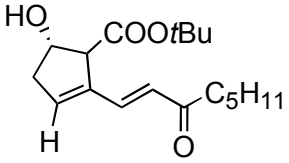
4-84b: R_f(hexane/EtOAc 2:1) = 0.47. - ^{1}H NMR (400 MHz): δ = 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.83 (s, 9H, SiC(C*H*$_3$)$_3$), 0.85 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.23-1.31 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.41 (s, 9H, OC(C*H*$_3$)$_3$), 1.58 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.80 (ddd, *J* = 14.1, 4.2, 2.3 Hz, 1H, C*H*$_2$CHOH), 2.14 (ddd, *J* = 14.1, 6.9, 5.5 Hz, 1H, C*H*$_2$CHOH), 2.47 (t, *J* = 7.4 Hz, 2H, C*H*$_2$CO), 2.55 (dd, *J* = 10.4, 5.2 Hz, 1H, C*H*COO*t*Bu), 3.18 (dt, *J* = 5.5, 9.5 Hz, 1H, C*H*CH=CH), 3.22 (d, *J* = 6.8 Hz, 1H, OH), 4.00 (m, 1H, C*H*OTBS), 4.40 (m, 1H, C*H*OH), 6.15 (dd, *J* = 15.7, 0.8 Hz, 1H, =C*H*CO), 6.64 (dd, *J* = 15.7, 8.8 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = –4.81 (q, Si(*C*H$_3$)$_2$), –4.76 (q, Si(*C*H$_3$)$_2$), 13.8 (q, CH$_2$*C*H$_3$), 17.9 (s, Si*C*(CH$_3$)$_3$), 22.4 (t, *C*H$_2$CH$_3$), 23.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.7 (q, SiC(*C*H$_3$)$_3$), 28.1 (q, OC(*C*H$_3$)$_3$), 31.4 (t, *C*H$_2$CH$_2$CH$_3$), 40.8 (t, CH$_2$*C*H$_2$CO), 43.3 (t, CH*C*H$_2$CH), 51.7 (d, CH*C*HCH=), 55.0 (d, *C*HCOO*t*Bu), 73.1 (d, *C*HOH), 77.4 (d, *C*HOTBS), 81.6 (s, O*C*(CH$_3$)$_3$), 130.5 (d, =*C*HCO), 145.8 (d, *C*H=CHCO), 170.8 (s, *C*OO*t*Bu), 200.2 (s, C=O).

4-83b: R_f(hexane/EtOAc 2:1) = 0.35. - ^{1}H NMR (400 MHz): δ = –0.005 (s, 3H, Si(C*H*$_3$)$_2$), 0.000 (s, 3H, Si(C*H*$_3$)$_2$), 0.82 (s, 10H, SiC(C*H*$_3$)$_3$, OH), 0.83 (m, 3H, CH$_2$C*H*$_3$), 1.24 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.35 (s, 9H, OC(C*H*$_3$)$_3$), 1.55 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.71 (dt, *J* = 13.9, 4.1 Hz, 1H, C*H*$_2$CHOH), 2.36 (m, *J* = 6.6 Hz, 1H, C*H*$_2$CHOH), 2.43 (t, *J* = 7.4 Hz, 2H, C*H*$_2$CO), 3.01 (dt, *J* = 3.4, 9.1 Hz, 1H, C*H*CH=CH), 3.07 (dd, *J* = 8.8, 4.3 Hz, 1H, C*H*COO*t*Bu), 4.09 (m, 1H, C*H*OTBS), 4.46 (m, 1H, C*H*OH), 6.08 (d, *J* = 15.8 Hz, 1H, =C*H*CO), 6.50 (dd, *J* = 15.8, 9.5 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = –4.98 (q, Si(*C*H$_3$)$_2$), –4.95 (q, Si(*C*H$_3$)$_2$), 13.7 (q, CH$_2$*C*H$_3$), 17.7 (s, Si*C*(CH$_3$)$_3$), 22.2 (t, *C*H$_2$CH$_3$), 23.6 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.5 (q, SiC(*C*H$_3$)$_3$), 27.9 (q, OC(*C*H$_3$)$_3$), 31.2 (t, *C*H$_2$CH$_2$CH$_3$), 40.1 (t, CH$_2$*C*H$_2$CO), 42.7 (t, CH*C*H$_2$CH), 53.0 (d, CH*C*HCH=), 56.9 (d, *C*HCOO*t*Bu), 73.4 (d, *C*HOH), 76.9 (d, *C*HOTBS), 81.2 (s, O*C*(CH$_3$)$_3$), 131.7 (d, =*C*HCO), 143.0 (d, *C*H=CHCO), 171.5 (s, *C*OO*t*Bu), 199.9 (s, C=O).

4-85b (detectable resonances): R_f(hexane/EtOAc=2:1) = 0.35. - ^{1}H NMR (400 MHz): δ = 1.37 (s, 9H, OC(C*H*$_3$)$_3$), 1.84 (m, 1H, C*H*$_2$CHOH), 2.04 (ddd, *J* = 14.2, 6.8, 3.7 Hz, 1H, C*H*$_2$CHOH), 2.72 (dt, *J* = 3.7, 9.1 Hz, 1H, C*H*CH=CH), 2.87 (dd, *J* = 9.6, 3.3 Hz, 1H,

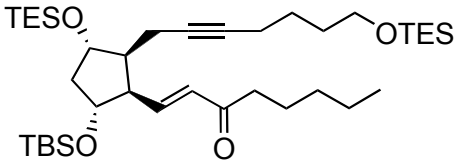
C*H*COO*t*Bu), 4.29 (br. t, *J* = 3.6 Hz, 1H, C*H*OTBS), 4.34 (m, 1H, C*H*OH), 6.07 (dd, *J* = 16.1, 0.7 Hz, 1H, =C*H*CO), 6.84 (dd, *J* = 16.0, 8.5 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = 43.9 (t, CH*C*H$_2$CH), 52.2 (d, CH*C*HCH=), 58.6 (d, *C*HCOO*t*Bu), 76.7 (d, *C*HOH), 77.2 (d, *C*HOTBS), 81.0 (s, O*C*(CH$_3$)$_3$), 131.5 (d, =*C*HCO), 144.8 (d, *C*H=CHCO), 170.4 (s, *C*OO*t*Bu), 200.1 (s, C=O).

***tert*-Butyl *(5S*)*-5-hydroxy-2-[(*E*)-3-oxooct-1-en-1-yl]cyclopent-2-ene-1-carboxylates:**



4-86 (detectable resonances): R$_f$(hexane/EtOAc2:1) = 0.35. - ^{1}H NMR (400 MHz): δ = 1.38 (s, 9H, OC(C*H*$_3$)$_3$), 3.47 (br. s, C*H*COO*t*Bu), 4.63 (br. d, *J* = 5.5 Hz, 1H, C*H*OH), 6.18 (d, *J* = 16.1 Hz, 1H, C*H*CO), 6.28 (br. s, 1H, CH$_2$C*H*=), 7.26 (d, *J* = 16.0 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = 43.0 (t, CH*C*H$_2$CH), 60.1 (d, *C*HCOO*t*Bu), 75.4 (d, *C*HOH), 127.5 (d, =*C*HCO), 136.7 (d, *C*H=CHCO), 140.5 (d, =*C*HCH$_2$CHOH), 200.6 (s, C=O).

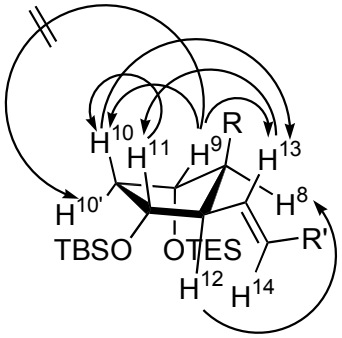
(1*R,2*R**,3*S**,4*S**)-1-(*tert*-Butyldimethylsilyloxy)-3-[7-(triethylsilyloxy)hept-2-yn-1-yl]-2-[(*E*)-3-(oxo)oct-1-en-1-yl]-4-(triethylsilyloxy)cyclopentane 4-87:**



*m*CPBA (70%, 11 mg, 0.043 mmol, 1.95 equiv.) was added to a solution of a mixture of 30 mg **4-6a** (17.2 mg, 0.021 mmol), and alkynes **4-9** and **4-74** (12.8 mg) in 3 mL dry CH$_2$Cl$_2$ at 0 °C. The reaction was monitored by TLC (hexane/ethyl acetate 20:1). After 20 min, the reaction was quenched with 5 mL concentrated Na$_2$S$_2$O$_3$ solution, diluted with ethyl acetate and stirred at r.t. for 10 min. The aqueous layer was extracted three times with ethyl acetate and three times with diethyl ether. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuum. The crude product was purified on a short column with hexane/ethyl acetate 50:1, gradient to 5:1. The product **4-87** (10 mg) eluted with hexane/ethyl acetate 50:1 and 20:1 (R$_f$ = 0.32). Yield 70%.

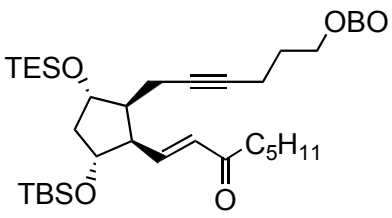
IR (ATR): $\tilde{\nu}$ = 2955 (s), 2933 (s), 2877 (m), 2860 (m), 1698 (w), 1676 (w), 1629 (w), 1462 (w), 1414 (w), 1379 (w), 1253 (w), 1105 (m), 1075 (m), 1008 (m), 979 (w), 837 (m), 777 (m), 743 (m). - MS(ESI) *m/z* (%): 701 (100) [M+H$^+$], 679 (20) [M$^+$], 547 (6), 489 (11). - HRMS: C$_{38}$H$_{75}$O$_4$Si$_3^+$: calc. 679.4973; found 679.4975; C$_{38}$H$_{75}$O$_4$Si$_3$Na$^+$: calc. 701.4793; found

701.4774. - ^{1}H NMR (400 MHz): δ = –0.009 (s, 3H, Si(CH_3)$_2$), 0.000 (s, 3H, Si(CH_3)$_2$), 0.56 (m, 12H, SiCH_2CH$_3$), 0.79 (t, *J* = 7.0 Hz, 3H, CH$_2$CH_3), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.96 (2xt, *J* = 7.9 Hz, 18H, SiCH$_2$CH_3), 1.18 (m, 4H, CH_2CH_2CH$_3$), 1.55-1.62 (m, 6H, CH_2CH_2CH$_2$OTES, CH_2CH$_2$CH$_2$CH$_3$), 1.77 (m, 1H, CHCHH^{α}CHOTES), 2.03 (m, 1H, CHCH_2C≡), 2.10 (m, 2H, CH$_2$CH_2C≡), 2.17 (m, 1H, CHCH_2C≡), 2.28 (t, *J* = 7.6 Hz, 2H, CH_2COCH=), 2.32 (m, 1H, CHCHH^{β}CHOTES), 2.37 (m, 1H, C*H*CH$_2$C≡), 3.01 (dt, *J* = 7.1, 8.5 Hz, 1H, C*H*CH=CH), 3.52 (t, *J* = 5.8 Hz, CH_2OTES), 4.03 (q, *J* = 6.6 Hz, 1H, C*H*OTBS), 4.14 (m, 1H, C*H*OTES), 6.17 (d, *J* = 15.6 Hz, 1H, C*H*CO), 6.90 (dd, *J* = 15.6, 9.7 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (100 MHz): δ = –4.41 (q, Si(*C*H$_3$)$_2$), –4.37 (q, Si(*C*H$_3$)$_2$), 4.8 (t, Si*C*H$_2$CH$_3$), 5.2 (t, Si*C*H$_2$CH$_3$), 7.1 (q, SiCH$_2$*C*H$_3$), 14.2 (q, CH$_2$*C*H$_3$), 18.2 (s, Si*C*(CH$_3$)$_3$), 18.9 (t, CH*C*H$_2$C≡), 19.0 (t, CH$_2$*C*H$_2$C≡), 22.9 (t, *C*H$_2$CH$_3$), 24.2 (t, *C*H$_2$*C*H$_2$CH$_2$C≡), 26.0 (q, SiC(*C*H$_3$)$_3$), 31.8 (t, *C*H$_2$CH$_2$CH$_3$), 32.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 41.2 (t, *C*H$_2$COCH=), 45.0 (t, CH*C*H$_2$CH), 50.8 (d, *C*HCH$_2$C≡), 53.2 (d, CH*C*HCH=), 62.4 (t, *C*H$_2$OTES), 75.2 (d, *C*HOTES), 78.8 (d, *C*HOTBS), 79.2 (s, *C*≡C), 81.9 (s, *C*≡C), 132.3 (d, CH=*C*HCO), 144.1 (d, *C*H=CHCO), 198.2 (s, C=O). - Significant NOESY interactions:

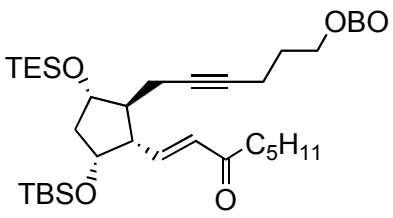


Synthesis of 4-89 from 4-6b in overall yield of 61% (see Scheme 4.34)

(1*R,2*R**,3*S**,4*S**)-1-(*tert*-Butyldimethylsilyloxy)-3-[6-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-yn-1-yl]-2-[(*E*)-3-(oxo)oct-1-en-1-yl]-4-(triethylsilyloxy)cyclopentane 4-90:**



4-90



12-*epi*-**4-90**

*m*CPBA (12 mg, 70% purity, 0.049 mmol, 2 equiv.) was added to a solution of **4-6b** (15α/β 1:1.6, 20 mg, 0.025 mmol) in 2.5 mL of dry CH_2Cl_2 at 0 °C. The reaction mixture was stirred until it was complete as indicated by TLC after 5 min (hexane/ethyl acetate 10:1

(R_f(substrates) = 0.45; R_f(product) = 0.28). After a total time of 15 min at 0 °C, the reaction miture was quenched with 3.5 mL saturated $Na_2S_2O_3$ solution and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 10 mg of crude product. The product was purified immediately by flash chromatography (hexane/ethyl acetate/Et_3N 20:1:1, and finally 10:1:1) to give 10.1 mg (61%) of an inseparable mixture of **4-90** and **12-*epi*-4-90** in a ratio of 4:1, R_f (hexane/ethyl acetate 5:1) = 0.51.

4-90: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.00 (s, 3H, $(OCH_2)_3CCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.65 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$), 0.87 (t, *J* = 6.8 Hz, 3H, $CH_2CH_2CH_3$), 0.97 (s, 9H, $SiC(CH_3)_3$), 1.04 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 1.25 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.69 (quint, *J* = 7.3 Hz, 2H, $=CHCOCH_2CH_2$), 1.82 (dt, *J* = 13.3, 6.0 Hz, 1H, $CHCH_2CH$), 2.00 (m, 3H, $CHCH_2C{\equiv}$, $CH_2CH_2C(OCH_2)_3$), 2.17 (m, 5H, $CHCH_2C{\equiv}CCH_2$, $CH_2C(OCH_2)_3$), 2.34-2.42 (m, 4H, $CHCH_2C{\equiv}$, $=CHCOCH_2$, $CHCH_2CH$), 3.07 (dt, *J* = 8.8, 6.9 Hz, 1H, CHCHOTBS), 3.56 (s, 6H, $CH_2C(OCH_2)_3$), 4.09 (q, *J* = 6.7 Hz, 1H, CHOTBS), 4.22 (dt, *J* = 6.6, 5.2 Hz, 1H, CHOTES), 6.26 (dd, *J* = 15.7, 0.7 Hz, 1H, =CHCO), 6.93 (dd, *J* = 15.7, 9.7 Hz, CH=CHCO). - ^{13}C NMR (300 MHz): δ = –4.42 (q, $SiCH_3$), –4.37 (q, $SiCH_3$), 5.2 (t, $SiCH_2CH_3$), 7.17 (q, $SiCH_2CH_3$), 13.9 (q, $(OCH_2)_3CCH_3$), 14.2 (q, $CH_2CH_2CH_3$), 18.2 (s, $SiC(CH_3)_3$), 18.8 (t, $CHCH_2C{\equiv}$), 19.0 (t, $CH_2CH_2C{\equiv}$), 23.0 (t, $CH_2CH_2CH_3$), 23.6 (t, $CH_2CH_2C{\equiv}$), 24.25 (t, $CH_2CH_2CH_2CH_3$), 26.0 (q, $SiC(CH_3)_3$), 29.88 (s, $(OCH_2)_3CCH_3$), 31.8 (t, $CH_2CH_2CH_3$), 36.52 (t, $CH_2C(OCH_2)_3$), 40.9 (t, $=CHCOCH_2$), 45.0 (t, $CHCH_2CH$), 50.7 (d, $CHCH_2C{\equiv}$), 53.1 (d, CHCHCH=), 72.4 (t, $CH_2C(OCH_2)_3$), 75.1 (d, CHOTES), 75.8 (d, CHOTBS), 79.3 (s, C≡C), 81.9 (s, C≡C), 109.4 (s, $CH_2C(OCH_2)_3$), 132.6 (d, =CHCO), 144.2 (d, CH=CHCO), 198.5 (s, CO).

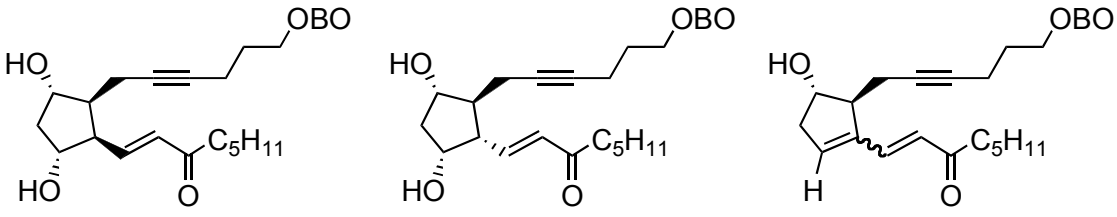
12-*epi*-4-90: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.00 (s, 3H, $(OCH_2)_3CCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.69 (q, *J* = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.87 (m, 3H, $CH_2CH_2CH_3$), 0.98 (s, 9H, $SiC(CH_3)_3$), 1.08 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 1.25 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.69 (m, 2H, $=CHCOCH_2CH_2$), 1.78 (ddd, *J* = 13.8, 6.0, 2.5 Hz, 1H, $CHCH_2CH$), 2.00 (m, 2H, $CH_2CH_2C(OCH_2)_3$), 2.17 (m, 4H, $\equiv CCH_2CH_2CH_2C(OCH_2)_3$), 2.21-2.31 (m, 3H, $CHCH_2C{\equiv}$, $CHCH_2CH$), 2.40 (m, 1H, $=CHCOCH_2$), 2.46 (m, 1H, $=CHCOCH_2$), 2.54 (m, 1H, $CHCH_2C{\equiv}$), 2.60 (ddd, *J* = 11.6, 9.4, 5.2 Hz, 1H, CHCHOTBS), 3.58 (s, 6H, $CH_2C(OCH_2)_3$), 3.99 (dt, *J* = 2.5, 5.5 Hz, 1H, CHOTBS), 4.26 (dt, *J* = 6.0, 8.2 Hz, 1H, CHOTES), 6.39 (d, *J* = 16.1 Hz, 1H, =CHCO), 7.03 (dd, *J* = 16.1, 9.3 Hz,

C*H*=CHCO). - ^{13}C NMR (300 MHz): δ = –4.8 (q, Si*C*H$_3$), –4.5 (q, Si*C*H$_3$), 5.3 (t, Si*C*H$_2$CH$_3$), 7.19 (q, SiCH$_2$*C*H$_3$), 13.9 (q, (OCH$_2$)$_3$C*C*H$_3$), 14.2 (q, CH$_2$CH$_2$*C*H$_3$), 18.2 (s, Si*C*(CH$_3$)$_3$), 18.3 (t, CH*C*H$_2$C≡), 18.9 (t, CH$_2$*C*H$_2$C≡), 22.9 (t, CH$_2$*C*H$_2$CH$_3$), 23.8 (t, *C*H$_2$CH$_2$C≡), 24.21 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.0 (q, SiC(*C*H$_3$)$_3$), 29.89 (s, (OCH$_2$)$_3$*C*CH$_3$), 31.9 (t, *C*H$_2$CH$_2$CH$_3$), 36.46 (t, *C*H$_2$C(OCH$_2$)$_3$), 39.9 (t, =CHCO*C*H$_2$), 45.5 (t, CH*C*H$_2$CH), 49.0 (d, *C*HCH$_2$C≡), 50.1 (d, CH*C*HCH=), 72.5 (t, CH$_2$C(O*C*H$_2$)$_3$), 74.2 (d, *C*HOTBS), 74.5 (d, *C*HOTES), 77.3 (s, *C*≡C), 82.7 (s, *C*≡C), 109.4 (s, CH$_2$*C*(OCH$_2$)$_3$), 132.4 (d, =*C*HCO), 145.5 (d, *C*H=CHCO), 198.8 (s, CO).

Table 6.8 NMR chemical shifts and multiplicities of compounds **4-90**, 12-*epi*-**4-90**, **4-89**, 12-*epi*-**4-89** and **4-91**

Compound/^{1}H NMR	H9	H11	H12	H13	H14	H15
4-90	4.22 (dt)	4.09 (q)	3.07 (dd)	6.93 (dd)	6.26 (dd)	-
12-*epi*-**4-90**	4.26 (dt)	3.99 (dt)	2.60 (ddd)	7.03 (dd)	5.39 (d)	-
4-89	3.95 (m)	3.79 (dd)	2.80 (m)	6.63 (dd)	6.12 (d)	-
12-*epi*-**4-89**	4.08 (m)	3.91 (br. s)	2.05-2.21 (m)	7.05 (dd)	6.15 (d)	-
4-91	4.37 (br. d)	5.73 (br. s)	-	6.04 (d)	7.29 (d)	-
Compound/^{13}C NMR	C9	C11	C12	C13	C14	C15
4-90	75.1 (d)	75.8 (d)	53.1 (d)	144.2 (d)	132.6 (d)	198.5 (d)
12-*epi*-**4-90**	74.5 (d)	74.2 (d)	50.1 (d)	145.5 (d)	132.4 (d)	198.8 (s)
4-89	75.9 (d)	75.5 (d)	53.36 (d)	143.7 (d)	132.2 (d)	198.6 (s)
12-*epi*-**4-89**	77.5 (d)	76.3 (d)	53.43 (d)	145.2 (d)	132.2 (d)	199.2 (s)
4-91	76.7 (d)	138.8 (d)	141.9 (s)	126.8 (d)	136.8 (d)	199.0 (s)

3-[6-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-yn-1-yl]-2-2-[(*E*)-3-(oxo)oct-1-en-1-yl]-1,4-cyclopentanediol 4-89:



4-89 12-*epi*-**4-89** **4-91**

A 4:1 mixture of orthoesters **4-90** and 12-*epi*-**4-90** (10 mg, 0.015 mmol) in 3 mL dry THF was treated at 0 °C with 0.075 mL (0.075 mmol) of a 1*M* TBAF solution in THF. The colour of the reaction mixture became dark orange after 3 min. The reaction was finished as indicated by TLC after 5 min (hexane/ethyl acetate 5:1). The reaction mixture was stirred at 0

°C for totally 30 min. It was diluted with 10 mL of a mixture diethyl ether/acetone/Et_3N 10:10:1 and filtered through a pad of silica gel. The solvent was concentrated in vacuum to give 11 mg of crude product. A TLC with CH_2Cl_2/acetone 2:1 showed three spots: R_f = 0.37, 0.48, 0.74. Flash chromatography (hexane/ethyl acetate/triethylamine 20:10:1, then 10:2:1 and finally 8:4:1) eluted 6.6 mg (100%) of ketones **4-89**, 12-*epi*-**4-89** and **4-91** in a ratio of 5:4:1. The products were well retained on silica and eluted in low concentration. Elution could not be detected by TLC, therefore the products were isolated as a mixture. Colourless oil, which displayed four spots on TLC: R_f(CH_2Cl_2/acetone 2:1) = 0.18, 0.39, 0.54, 0.79. A fourth minor component in this mixture was also detected in the NMR spectra.

4-89: ^{1}H NMR (600 MHz, C_6D_6): δ = –0.02 (s, 3H, $(OCH_2)_3CCH_3$), 0.88 (m, 3H, $CH_2CH_2CH_3$), 1.17-1.50 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.62 (m, 3H, =CHCOCH$_2$CH_2, CHCH_2CH), 1.85 (m, 1H, CHCH_2C≡), 1.88-2.00 (m, 3H, CHCH_2C≡, CH_2CH$_2$C(OCH$_2$)$_3$), 2.05-2.21 (m, 5H, CHCH_2CH, ≡CCH_2CH$_2$CH_2C(OCH$_2$)$_3$), 2.24-2.42 (m, 3H, CHCH$_2$C≡, =CHCOCH_2), 2.80 (m, 1H, CHCH=CHCO), 3.54 (s, 6H, CH$_2$C(OCH_2)$_3$), 3.79 (dt, *J* = 5.4, 6.1 Hz, 1H, CHCHCH=), 3.95 (m, 1H, CHCHCH$_2$C≡), 6.12 (d, *J* = 15.7 Hz, 1H, =CHCO), 6.63 (dd, *J* = 15.7, 9.5 Hz, CH=CHCO). - ^{13}C NMR (150 MHz): δ = 13.9 (q, $(OCH_2)_3CCH_3$), 14.2 (q, $CH_2CH_2CH_3$), 18.7 (t, CH_2CH_2C≡), 19.3 (t, CHCH_2C≡), 22.94 (t, $CH_2CH_2CH_3$), 23.6 (t, CH_2CH$_2$C≡), 24.1 (t, CH_2CH$_2$CH$_2$CH$_3$), 29.8 (s, $(OCH_2)_3CCH_3$), 31.81 (t, CH_2CH$_2$CH$_3$), 36.20 (t, CH_2C(OCH$_2$)$_3$), 39.9 or 40.8 (t, =CHCOCH_2), 42.9 (t, CHCH_2CH), 50.8 (d, CHCH$_2$C≡), 53.36 (d, CHCHCH=), 72.4 (t, CH$_2$C(OCH_2)$_3$), 75.5 (d, HOCHCHCH=), 75.9 (d, CHCHCH$_2$C≡), 78.4 (s, C≡C), 79.5 (s, C≡C), 109.46 (s, CH$_2$C(OCH$_2$)$_3$), 132.20 (d, =CHCO), 143.7 (d, CH=CHCO), 198.6 (s, CO).

12-*epi*-4-89: ^{1}H NMR (600 MHz, C_6D_6): δ = –0.04 (s, 3H, $(OCH_2)_3CCH_3$), 0.88 (m, 3H, $CH_2CH_2CH_3$), 1.17-1.50 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.62 (m, 2H, =CHCOCH$_2$CH_2), 1.76-1.86 (m, 2H, CHCH_2CH), 1.88-2.00 (m, 3H, CHCH_2C≡, CH_2CH$_2$C(OCH$_2$)$_3$), 2.05-2.21 (m, 6H, CHCH=CHCO, CHCH$_2$C≡CCH_2CH$_2$CH_2C(OCH$_2$)$_3$), 2.24-2.43 (m, 3H, =CHCOCH_2, CHCH_2C≡), 3.54 (s, 6H, CH$_2$C(OCH_2)$_3$), 3.91 (br. s, HOCHCHCH=), 4.08 (m, 1H, CHCHCH$_2$C≡), 6.15 (d, *J* = 16.1 Hz, 1H, =CHCO), 7.05 (dd, *J* = 16.1, 8.2 Hz, CH=CHCO). - ^{13}C NMR (300 MHz): δ = 13.9 (q, $(OCH_2)_3CCH_3$), 14.2 (q, $CH_2CH_2CH_3$), 18.8 (t, CH_2CH_2C≡), 20.9 (t, CHCH_2C≡), 22.95 (t, $CH_2CH_2CH_3$), 23.5 (t, CH_2CH$_2$C≡), 24.1 (t, CH_2CH$_2$CH$_2$CH$_3$), 29.8 (s, $(OCH_2)_3CCH_3$), 31.83 (t, CH_2CH$_2$CH$_3$), 36.18 (t, CH_2C(OCH$_2$)$_3$), 39.9 or 40.8 (t, =CHCOCH_2), 43.5 (t, CHCH_2CH), 51.2 (d, CHCH$_2$C≡), 53.44 (d, CHCHCH=), 72.4 (t, CH$_2$C(OCH_2)$_3$), 76.3 (d, HOCHCHCH=), 77.5 (d, CHCHCH$_2$C≡), 81.8

(s, *C*≡C), 82.0 (s, *C*≡C), 109.43 (s, $CH_2C(OCH_2)_3$), 132.24 (d, =*C*HCO), 145.2 (d, *C*H=CHCO), 199.2 (s, CO).

4-91, detectable resonances: ^{1}H NMR (600 MHz, C_6D_6): δ = 2.19 (m, 1H, CHC*H*$_2$CH), 2.53 (m, 1H, CHC*H*$_2$CH), 4.37 (br. d, *J* = 5.9 Hz, 1H, C*H*CHCH$_2$C≡), 5.73 (br. s, C*H*=CCH=), 6.04 (d, *J* = 16.2 Hz, C*H*=CHCO), 7.29 (d, *J* = 16.1 Hz, 1H, =C*H*CO). - ^{13}C NMR (150 MHz): δ = 41.9 (t, CH*C*H$_2$CH), 76.7 (d, *C*HCHCH$_2$C≡), 78.8 (s, *C*≡C), 82.0 (s, *C*≡C), 109.5 (s, $CH_2C(OCH_2)_3$), 126.8 (d, *C*H=CHCO), 136.8 (d, =*C*HCO), 138.8 (d, *C*H=CCH=CHCO), 141.9 (s, =*C*CH=CHCO), 199.0 (s, CO).

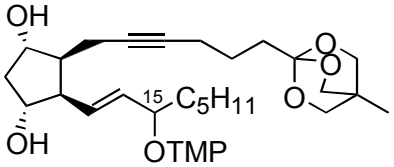
Synthesis of 4-92 from 4-6b (path I, II and III, see Scheme 4.35)

Table 6.9 *Optimisation of the conversion of OBO esters to methyl esters*

Entry (Path)	Yield	Conditions
1 (I)	**4-92** from **4-88** 98%	1) TBAF; 2) 0.078 mmol; 0.3 mL 0.28*M* $NaHSO_4$ (0.2 equiv.), 3.7 mL DME, no workup; $LiOH·H_2O$ 24 equiv., 2 mL H_2O, workup; esterification.
2 (II)	**4-92** from **4-88** 45%	0.035 mmol; 10 mL 0.15*M* $NaHSO_4$ (4.3 equiv.), 3 mL DME, workup; $LiOH·H_2O$ 50 equiv., THF 5 mL, 1.5 mL H_2O, workup; esterification
3 (III)	**4-78** from **4-6b** 62% (+6% of **4-92**)	0.232 mmol; 0.3 mL 0.14*M* $NaHSO_4$ (0.18 equiv.), 4 mL DME, 1.8 equiv. $LiOH·H_2O$, 1 mL H_2O, workup: no saponification occurred; 6 equiv. $LiOH·H_2O$, 5 mL DME, 2 mL H_2O, workup; esterification; acidic workup.

Path I: Synthesis of 4-92 from 4-6b in 98% yield (see Scheme 4.35)

Deprotection of 4-6b to the corresponding diol 4-88 (The same procedure was also used to deprotect **4-75** and mixtures of **4-6a/4-75**):



A mixture of orthoester **4-6b** (15α/β 1.2:1, 45 mg, 0.056 mmol) and 1-(5-triethylsilyl-4-pentynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane **4-76** (35 mg, 0.113 mmol) in 4.5 mL dry THF was treated at 0 °C with 1.7 mL (1.7 mmol) of a 1*M* TBAF solution in THF. The reaction mixture was stirred for 4.5 h at 0 °C, when it was complete as indicated by TLC. The reaction miture was quenched with 5 mL of saturated NH_4Cl solution, 2 mL of water and

diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether and once with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated to give 130 mg of crude product. Flash chromatography (hexane/ethyl acetate/triethylamine 100:20:3) eluted 20 mg (90%) of hexynoic acid orthoester **4-10**, on changing to CH_2Cl_2/acetone/triethylamine 25:5:1 and 10:5:1, 32 mg (100% yield) of pure **4-88** as an inseparable mixture of 15α/15β-isomers in a 1:1 ratio was isolated as a colourless oil, R_f(CH_2Cl_2/acetone 2:1) = 0.65, 0.56; R_f(ethyl acetate) = 0.55, 0.45. The stereochemistry of the 15-position could not be assigned.

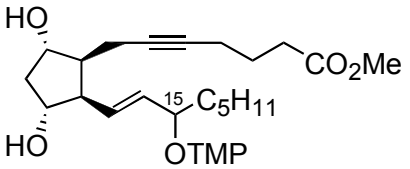
15α-/15β-**4-88**: IR (Film): $\tilde{\nu}$ = 3400 cm^{-1} (br. w), 2929 (s), 2874 (m), 1461 (w), 1398 (w), 1377 (w), 1356 (w), 1265 (w), 1186 (w), 1133 (w), 1058 (s), 991 (m), 958 (s). - MS(ESI) *m/z* (%): 598 (38) [M+Na^+], 576 (100) [M+H^+]. - HRMS: $C_{34}H_{58}NO_6^+$: calc. 576.4264; found 576.4257.

4-88-Isomer 1: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.01 (s, 3H, $(OCH_2)_3CCH_3$), 0.93 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.12-1.42 (m, 21H, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$, $CH_2(CH_2)_3CH_3$), 1.43-1.63 (m, 4H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$), 1.83 (m, 2H, $CH_2CHOTMP$, $CHCH_2CH$), 1.93 (m, 2H, $CH_2CH_2C{\equiv}$), 2.09-2.25 (m, 6H, $CH_2C{\equiv}CCH_2CH_2CH_2$), 2.33 (m, 1H, $CHCH_2CH$), 2.42 (m, 1H, $CHCH_2C{\equiv}$), 2.80 (br. s, 2H, OH), 2.89 (m, 1H, $HOCHCHCH{=}$), 3.55 (s, 6H, $CH_2C(OCH_2)_3$), 4.00 (m, 1H, $HOCHCHCH{=}$), 4.08 (dt, *J* = 7.3, 5.1 Hz, 1H, $HOCHCHCH_2$), 4.22 (m, 1H, $CHOTMP$), 5.31 (dd, *J* = 15.4, 9.0 Hz, 1H, $CH{=}CHCHOTMP$), 5.57 (dd, *J* = 15.4, 8.9 Hz, 1H, $={CH}CHOTMP$). - ^{13}C NMR (150 MHz): δ = 13.9 (q, $(OCH_2)_3CCH_3$), 14.3 (q, CH_2CH_3), 17.7 (t, $NCCH_2CH_2$), 18.9 (t, $CHCH_2C{\equiv}$), 19.59 (t, $CH_2CH_2C{\equiv}$), 20.6 (q, $NC(CH_3)_2$), 20.7 (q, $NC(CH_3)_2$), 23.1 (t, CH_2CH_3), 23.6 (t, $CH_2CH_2C{\equiv}$), 25.78 (t, $CH_2CH_2CH_2CH_3$), 29.86 (s, $(OCH_2)_3CCH_3$), 32.4 (t, $CH_2CH_2CH_3$), 34.6 (q, $NC(CH_3)_2$), 35.02 (t, $CH_2CHOTMP$), 35.6 (q, $NC(CH_3)_2$), 36.2 (t, $CH_2C(OCH_2)_3$), 40.4 (t, $NCCH_2CH_2$), 40.7 (t, $NCCH_2CH_2$), 42.8 (t, $CHCH_2CH$), 50.4 (d, $CHCH_2C{\equiv}$), 54.5 (d, $CHCHCH{=}$), 59.3 (s, $NC(CH_3)_2$), 60.5 (s, $NC(CH_3)_2$), 72.42 (t, $CH_2C(OCH_2)_3$), 76.0 (d, $HOCHCHCH{=}$), 76.28 (d, $HOCHCHCH_2$), 80.1 (s, $C{\equiv}C$), 81.2 (s, $C{\equiv}C$), 85.8 (d, $CHOTMP$), 109.5 (s, $CH_2C(OCH_2)_3$), 130.4 (d, $CH{=}CHCHOTMP$), 136.3 (d, $={CH}CHOTMP$).

4-88-Isomer 2: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.00 (s, 3H, $(OCH_2)_3CCH_3$), 0.90 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.12-1.42 (m, 21H, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$, $CH_2(CH_2)_3CH_3$), 1.43-1.63 (m, 4H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$), 1.83 (m, 2H, $CH_2CHOTMP$, $CHCH_2CH$), 1.93 (m, 2H, $CH_2CH_2C{\equiv}$), 2.09-2.25 (m, 6H, $CH_2C{\equiv}CCH_2CH_2CH_2$), 2.33 (m, 1H, $CHCH_2CH$), 2.50 (m, 1H, $CHCH_2C{\equiv}$), 2.80 (br. s, 2H, OH), 2.89 (m, 1H, $HOCHCHCH{=}$),

3.54 (s, 6H, $CH_2C(OCH_2)_3$), 3.96 (ddd, *J* = 10.8, 7.2, 4.6 Hz, 1H, HOC*H*CHCH=), 4.18 (dt, *J* = 7.2, 4.5 Hz, 1H, HOC*H*CHCH$_2$), 4.22 (m, 1H, C*H*OTMP), 5.28 (dd, *J* = 15.4, 9.7 Hz, 1H, C*H*=CHCHOTMP), 5.60 (dd, *J* = 15.3, 9.0 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz): δ = 13.9 (q, $(OCH_2)_3CCH_3$), 14.4 (q, CH_2CH_3), 17.7 (t, $NCCH_2CH_2$), 18.8 (t, $CHCH_2C{\equiv}$), 19.64 (t, $CH_2CH_2C{\equiv}$), 20.8 (q, $NC(CH_3)_2$), 23.1 (t, CH_2CH_3), 23.6 (t, $CH_2CH_2C{\equiv}$), 25.81 (t, $CH_2CH_2CH_2CH_3$), 29.87 (s, $(OCH_2)_3CCH_3$), 32.4 (t, $CH_2CH_2CH_3$), 34.3 (q, $NC(CH_3)_2$), 35.1 (t, CH_2CHOTMP), 35.3 (q, $NC(CH_3)_2$), 36.2 (t, $CH_2C(OCH_2)_3$), 40.46 (t, $NCCH_2CH_2$), 40.50 (t, $NCCH_2CH_2$), 43.0 (t, $CHCH_2CH$), 50.8 (d, $CHCH_2C{\equiv}$), 53.9 (d, CHCHCH=), 59.4 (s, $NC(CH_3)_2$), 60.6 (s, $NC(CH_3)_2$), 72.41 (t, $CH_2C(OCH_2)_3$), 76.34 (d, $HOCHCHCH_2$), 76.41 (d, HOCHCHCH=), 80.3 (s, C≡C), 81.3 (s, C≡C), 85.3 (d, CHOTMP), 109.5 (s, $CH_2C(OCH_2)_3$), 130.9 (d, CH=CHCHOTMP), 135.9 (d, =CHCHOTMP).

Methyl 7-[(1*S,2*R**,3*R**,5*S**)-3,5-dihydroxy-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentyl]hept-5-ynoate 4-92:**



$NaHSO_4$ (10 mg, 0.083 mmol, 1.5 equiv.) was added at 0 °C to a solution of diol **4-88** (32 mg, 0.056 mmol) resulting from deprotection of **4-6b/4-75** in 3.7 mL DME and 0.3 mL water. The solution was stirred at 0 °C for 45 min and at r.t. for 20 min. Then LiOH (78 mg, 1.85 mmol, 33 equiv.) was added and the reaction mixture was stirred at 0 °C for 2 h and finally at r.t. for 0.5 h. It was diluted with ethyl acetate and acidified with 4.5*M* HCl solution to pH 1. The layers were separated. The aqueous layer was extracted three times with ethyl acetate and three times with diethyl ether. The combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give 45 mg of the acid as a very thick oil, which was difficult to dissolve in any solvent later on. Therefore, the esterification was performed immediately in the same flask. The crude acid was dissolved in 3 mL of dry THF and 0.8 mL of dry MeOH under a nitrogen atmosphere. To this solution 0.59 mL (1.2 mmol) of a 2*M* solution of $TMSCHN_2$ in diethyl ether was added and the reaction was stirred at r.t. for 2 h 15 min. The reaction was quenched carefully with 3.5 mL of a 2*M* HCl solution and stirred for 5 min. The aqueous layer was extracted three times with ethyl acetate and three times with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give the crude product (60 mg). Purification by flash chromatography (ethyl acetate/acetone 50:1, gradient to 20:1 and 10:1; the product eluted with 20:1) gave 28 mg

(98% yield based on **4-6b**+**4-75**) of pure **4-92** as an inseparable mixture of 15α/15β-isomers. The diastereomeric ratio was 1:1. The configuration in 15-position could not be established. R_f(ethyl acetate) = 0.66 and 0.60, R_f(CH_2Cl_2/acetone (1:1) = 0.78 and 0.72. Both isomers are well retained on silica and elute only in the presence of acetone.

15α-/15β-**4-92:** IR (Film): $\tilde{\nu}$ = 3402 cm^{-1} (br. w), 2929 (s), 2870 (m), 1740 (s), 1456 (m), 1437 (m), 1375 (m), 1360 (m), 1242 (m), 1160 (m), 1134 (m), 1082 (m), 974 (m). - MS(ESI) *m/z* (%): 1033 (38) [2M+Na^+], 528 (100) [M+Na^+], 506 (67) [M+H^+], 372 (43) [M–TEMPO+Na^+], 158 (18) [$TEMPOH_2$]$^+$. - HRMS: $C_{30}H_{51}NO_5Na^+$: calc. 528.3665; found 528.3665.

4-92-*Major isomer:* ^{1}H NMR (600 MHz, C_6D_6): δ = 0.67 (br. s, 2H, O*H*), 0.91 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.15-1.30 (m, 13H, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$), 1.27-1.41 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$, $NCCH_2CH_2CH_2CN$), 1.45-1.59 (m, 4H, $NCCH_2CH_2CH_2CN$, TMPOCHCH_2), 1.68 (m, 3H, $CHCH_2CH$, CH_2CH_2COOMe), 1.84 (m, 1H, TMPOCHCH_2), 2.01 (m, 2H, $\equiv CCH_2CH_2$), 2.15 (ddt, *J* = 15.1, 6.6, 2.3 Hz, 1H, $CHCH_2C\equiv$), 2.24 (t, *J* = 7.3 Hz, 2H, CH_2COOMe), 2.24 (m, 1H, $CHCH_2CH$), 2.40 (m, 2H, $CHCH_2C\equiv$), 2.78 (m, 1H, HOCHC*H*CH=), 3.31 (s, 3H, OCH_3), 3.85 (dt, *J* = 6.3, 4.4 Hz, 1H, HOC*H*CHCH=), 4.07 (dt, *J* = 7.2, 4.7 Hz, 1H, $HOCHCHCH_2$), 4.22 (m, 1H, C*H*OTMP), 5.25 (dd, *J* = 15.3, 9.3 Hz, 1H, C*H*=CHCHOTMP), 5.53 (dd, *J* = 15.5, 8.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz): δ = 14.3 (q, CH_2CH_3), 17.74 (t, $NCCH_2CH_2CH_2CN$), 18.38 (t, $CH_2CH_2C\equiv$), 19.58 (t, $CHCH_2C\equiv$), 20.64 (q, $NC(CH_3)_2$), 20.7 (q, $NC(CH_3)_2$), 23.10 (t, CH_2CH_3), 24.5 (t, CH_2CH_2COOMe), 25.82 (t, $CH_2CH_2CH_2CH_3$), 32.3 (t, $CH_2CH_2CH_3$), 32.8 (t, CH_2COOMe), 34.5 (q, $NC(CH_3)_2$), 35.02 (t, $TMPOCHCH_2$), 35.2 (q, $NC(CH_3)_2$), 40.48 (t, $NCCH_2CH_2CH_2CN$), 40.66 (t, $NCCH_2CH_2CH_2CN$), 42.9 (t, $CHCH_2CH$), 50.4 (d, $CHCH_2C\equiv$), 51.1 (q, OCH_3), 53.9 (d, $CHCHCH=$), 59.3 (s, $NC(CH_3)_2$), 60.5 (s, $NC(CH_3)_2$), 76.3 (d, $HOCHCHCH=$), 76.4 (d, $HOCHCHCH_2$), 80.3 (s, $C\equiv C$), 80.8 (s, $C\equiv C$), 85.3 (d, CHOTMP), 130.6 (d, $CH=CHCHOTMP$), 136.1 (d, $=CHCHOTMP$), 173.11 (s, COOMe).

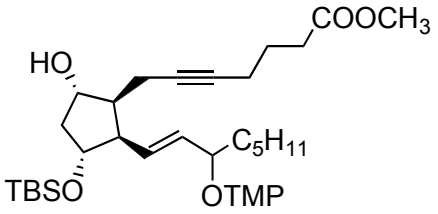
4-92-*Minor isomer*: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.67 (br. s, 2H, O*H*), 0.92 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.15-1.30 (m, 13H, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$), 1.27-1.41 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$, $NCCH_2CH_2CH_2CN$), 1.45-1.59 (m, 4H, $NCCH_2CH_2CH_2CN$, TMPOCHCH_2), 1.68 (m, 3H, $CHCH_2CH$, CH_2CH_2COOMe), 1.84 (m, 1H, TMPOCHCH_2), 2.01 (m, 2H, $\equiv CCH_2CH_2$), 2.06 (ddt, *J* = 16.5, 8.7, 2.3 Hz, 1H, $CHCH_2C\equiv$), 2.24 (t, *J* = 7.3 Hz, 2H, CH_2COOMe), 2.24 (m, 1H, $CHCH_2CH$), 2.34 (m, 1H, $CHCH_2C\equiv$), 2.40 (m, 1H, $CHCH_2C\equiv$), 2.78 (m, 1H, HOCHC*H*CH=), 3.32 (s, 3H, OCH_3), 3.91 (m, 1H,

HOC*H*CHCH=), 3.97 (dt, *J* = 7.2, 5.2 Hz, 1H, HOC*H*CHCH$_2$), 4.22 (m, 1H, C*H*OTMP), 5.24 (dd, *J* = 15.2, 9.3 Hz, 1H, C*H*=CHCHOTMP), 5.56 (dd, *J* = 15.9, 9.9 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz): δ = 14.3 (q, CH$_2$*C*H$_3$), 17.65 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.34 (t, CH$_2$*C*H$_2$C≡), 19.62 (t, CH*C*H$_2$C≡), 20.61 (q, NC(*C*H$_3$)$_2$), 20.7 (q, NC(*C*H$_3$)$_2$), 23.13 (t, *C*H$_2$CH$_3$), 24.5 (t, *C*H$_2$CH$_2$COOMe), 25.77 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 32.34 (t, *C*H$_2$CH$_2$CH$_3$), 32.8 (t, *C*H$_2$COOMe), 34.3 (q, NC(*C*H$_3$)$_2$), 35.04 (t, TMPOCH*C*H$_2$), 35.6 (q, NC(*C*H$_3$)$_2$), 40.40 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.47 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 42.8 (t, CH*C*H$_2$CH), 50.1 (d, *C*HCH$_2$C≡), 51.1 (q, O*C*H$_3$), 54.4 (d, CH*C*HCH=), 59.4 (s, N*C*(CH$_3$)$_2$), 60.6 (s, N*C*(CH$_3$)$_2$), 75.9 (d, HO*C*HCHCH=), 76.3 (d, HO*C*HCHCH$_2$), 80.2 (s, *C*≡C), 80.5 (s, *C*≡C), 85.6 (d, *C*HOTMP), 130.1 (d, *C*H=CHCHOTMP), 136.5 (d, =*C*HCHOTMP), 173.08 (s, *C*OOMe).

Path III: Synthesis of 4-92 from 4-6b in overall yield of 43% (see Scheme 4.35)

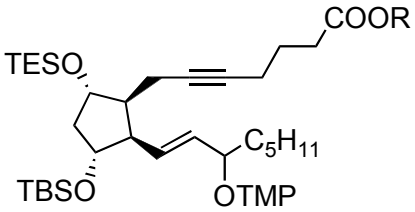
1) Conversion of **4-6b** to the corresponding methyl ester **4-78** (62%); 2) Methyl ester **4-78** was deprotected with TBAF to diol **4-92** (70%).

Methyl 7-[(1*S,2*R**,3*R**,5*S**)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentyl]hept-5-ynoate 4-78**

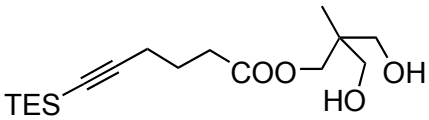


To a mixture of **4-6b** (15α/β 1.2:1, 62.8 mg, 0.078 mmol) and TES-alkyne **4-76** (47.2 mg, 0.152 mmol) in 4 mL DME 0.3 mL of a 0.14 *M* aqueous solution of $NaHSO_4$ (5 mg, 0.042 mmol, 0.18 equiv. based on substrates) was added and the solution was stirred at 0 °C for 30 min. The consumption of the substrate was monitored by TLC with hexane/ethyl acetate 10:1. Then 1 mL of a 0.42 *M* aqueous solution of LiOH (17.5 mg, 0.42 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h 40 min and at r.t. for 50 min. TLC with CH_2Cl_2/acetone 5:1 showed two spots at R_f = 0.48 and 0.93. The reaction mixture was diluted with 3 mL of ethyl acetate. The organic layer was extracted twice with 3 mL of water and once with 3 mL of 0.3 *M* LiOH solution. The organic layer, which contained a solid residue was filtered through cotton and concentrated in vacuum to give 120 mg of a mixture of **K** and **H** (R_f with hexane/ethyl acetate 5:1 = 0.58). Surprisingly the ^{13}C NMR spectrum of the crude product displayed four triplets at 65.9, 66.8, 67.0 and 68.1, which could correspond to the methylene positions in the ester unit COO*C*H$_2$C(*C*H$_2$OH)CH$_3$. Probably ester **G** was not

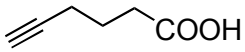
completely saponified, and still present in the mixture. The combined aqueous layers were acidified with $NaHSO_4$ solution to pH 3, and then it was extracted with ethyl acetate and diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give 30 mg of a mixture of acids **I** and **J**.



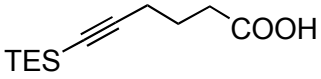
G R = $CH_2C(CH_2OH)CH_3$
K R = H



H



I



J

The saponification of the crude mixture of **K**, **G** and **H** was repeated. To a solution of 120 mg of this mixture in 5 mL DME and 2 mL of water 60 mg (1.43 mmol) of LiOH was added at r.t. (pH 10) and the reaction was stirred at this temperature for 6.5 h. The reaction mixture was diluted with ethyl acetate and the layers were separated. The organic layer (Organic layer 1 OL1) was extracted 3 times with water and preserved.

1) The combined aqueous phases were acidified with 430 mg $NaHSO_4$ to pH 2 and extracted three times with ethyl acetate and once with diethyl ether. The organic layers (OL 2) were dried over Na_2SO_4 and concentrated in vacuum to give 12 mg of the acid **J**.

2) Organic layer 1 OL1 was diluted with diethyl ether and stirred for 15 min with 2 mL of a 2.5 *M* $NaHSO_4$ solution. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuum to give 55 mg of the crude acid **K (**TLC with hexane/ethyl acetate 2:1 gives two spots with R_f = 0.69 and respectively R_f = 0.50; TLC with hexane/ethyl acetate 5:1 gives two spots with R_f = 0.55 and respectively R_f = 0.13).

The crude acid **K** (55 mg) was dissolved in 5 mL dry THF and 0.5 mL dry MeOH under a nitrogen atmosphere. To this solution 0.39 mL (0.78 mmol) of a 2*M* solution of $TMSCHN_2$ in diethyl ether was added and the reaction was stirred at r.t. for 3.5 h. The reaction was quenched carefully with 5 mL of a 1.2*M* HCl solution, diluted with diethyl ether and stirred for 5 min. The aqueous layer was extracted three times with ethyl acetate and once with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give the crude product (90 mg). Purification by flash

chromatography (hexane/ethyl acetate 20:1, gradient to 5:1, 2.5:1 and pure EtOAc; the product eluted with 2.5:1 and pure EtOAc) gave 30 mg (62% yield based on **4-6b**) of pure **4-78** as an inseparable mixture of 15α/15β-isomers in a 1:1 ratio, R_f(hexane/ethyl acetate 5:1) = 0.40. Flashing the column with acetone gave a fraction of 10 mg containing aproxim. 3 mg of impure deprotected diol **4-92** (6% yield).

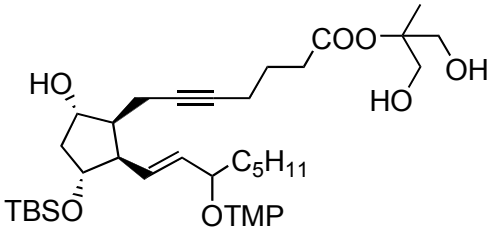
4-78-*Isomer I:* ^{1}H NMR (400 MHz, C_6D_6): δ = –0.01 (s, 3H, SiC*H*$_3$), 0.00 (s, 3H, SiC*H*$_3$), 0.84 (m, 3H, CH_2CH_3), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 1.11-1.37 (m, 23H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, NC(C*H*$_3$)$_2$, $CH_2CH_2CH_2CH_2CH_3$), 1.42-1.55 (m, 2H, $NCCH_2CH_2CH_2CN$, C*H*$_2$CHOTMP), 1.58 or 1.59 (quint, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_2$COOMe), 1.62-1.84 (m, 2H, C*H*$_2$CHOTMP, CHC*H*$_2$CH), 1.92 (m, 2H, ≡CC*H*$_2$CH$_2$), 2.16 (t, *J* = 7.3 Hz, 2H, C*H*$_2$COOMe), 2.22 (m, 2H, CHC*H*$_2$CH, CHC*H*$_2$C≡), 2.34 (m, 1H, CHC*H*$_2$C≡), 2.39 (m, 1H, C*H*CH$_2$C≡), 2.89 (m, 1H, =CHC*H*CHOTBS), 3.237 (s, 3H, COOC*H*$_3$), 3.92 (dt, *J* = 6.1, 4.3 Hz, 1H, C*H*OTBS), 4.00 (m, 1H, C*H*OH), 4.17 (m, 1H, C*H*OTMP), 5.22 (dd, *J* = 15.3, 9.6 Hz, 1H, C*H*=CHCHOTMP), 5.48 (dd, *J* = 14.9, 8.9 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 14.3 (q, CH_2CH_3), 17.7 (t, $NCCH_2CH_2CH_2CN$), 18.4 (s, SiC(*C*H$_3$)$_3$), 18.42 (t, $CH_2CH_2C{\equiv}$), 19.7 (t, CH*C*H$_2$C≡), 20.7 (q, NC(*C*H$_3$)$_2$), 23.1 (t, *C*H$_2$CH$_3$), 24.59 (t, *C*H$_2$CH$_2$COOMe), 25.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.10 (q, C(*C*H$_3$)$_3$), 32.4 (t, *C*H$_2$CH$_2$CH$_3$), 32.84 (t, *C*H$_2$COOMe), 34.4 (q, NC(*C*H$_3$)$_2$), 35.11 (t, *C*H$_2$CHOTMP), 35.9 (q, NC(*C*H$_3$)$_2$), 40.5 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.6 (t, $NCCH_2CH_2CH_2CN$), 44.0 (t, CH*C*H$_2$CH), 50.2 (d, *C*HCH$_2$C≡), 51.0 (q, O*C*H$_3$), 54.4 (d, =CH*C*HCHOTBS), 60.5 (s, N*C*(CH$_3$)$_2$), 76.5 (d, *C*HOH), 77.3 (d, *C*HOTBS), 80.48 (s, *C*≡C), 80.8 (s, *C*≡C), 85.2 (d, *C*HOTMP), 129.4 (d, *C*H=CHCHOTMP), 136.1 (d, =*C*HCHOTMP), 172.9 (s, *C*OOMe).

4-78-*Isomer II:* ^{1}H NMR (400 MHz, C_6D_6): δ = 0.01 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$), 0.84 (m, 3H, CH_2CH_3), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 1.11-1.37 (m, 23H, NCC*H*$_2$C*H*$_2$C*H*$_2$CN, NC(C*H*$_3$)$_2$, $CH_2CH_2CH_2CH_2CH_3$), 1.42-1.55 (m, 2H, $NCCH_2CH_2CH_2CN$, C*H*$_2$CHOTMP), 1.58 or 1.59 (quint, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_2$COOMe), 1.62-1.84 (m, 2H, C*H*$_2$CHOTMP, CHC*H*$_2$CH), 1.92 (m, 2H, ≡CC*H*$_2$CH$_2$), 2.10 (m, 2H, CHC*H*$_2$CH, CHC*H*$_2$C≡), 2.16 (t, *J* = 1.0, 7.3 Hz, 2H, C*H*$_2$COOMe), 2.37-2.47 (m, 2H, C*H*C*H*$_2$C≡), 2.89 (m, 1H, =CHC*H*CHOTBS), 3.243 (s, 3H, COOC*H*$_3$), 3.85 (m, 1H, C*H*OH), 4.00 (m, 1H, C*H*OTBS), 4.12 (dt, *J* = 4.7, 8.6 Hz, 1H, C*H*OTMP), 5.06 (dd, *J* = 15.3, 9.9 Hz, 1H, C*H*=CHCHOTMP), 5.49 (dd, *J* = 15.1, 8.7 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (100 MHz): δ = 14.3 (q, CH_2CH_3), 17.8 (t, $NCCH_2CH_2CH_2CN$), 18.3 (s, SiC(*C*H$_3$)$_3$), 18.37 (t, $CH_2CH_2C{\equiv}$), 19.6 (t, CH*C*H$_2$C≡), 20.5 (q, NC(*C*H$_3$)$_2$), 23.2 (t, *C*H$_2$CH$_3$), 24.57 (t, *C*H$_2$CH$_2$COOMe), 25.8 (t,

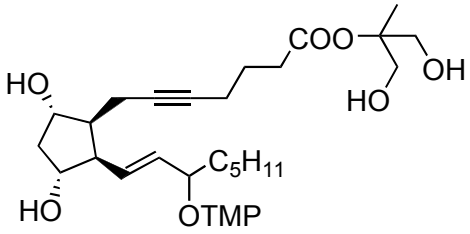
*C*H$_2$CH$_2$CH$_2$CH$_3$), 26.13 (q, C(*C*H$_3$)$_3$), 32.4 (t, *C*H$_2$CH$_2$CH$_3$), 32.86 (t, *C*H$_2$COOMe), 34.4 (q, NC(*C*H$_3$)$_2$), 35.14 (t, *C*H$_2$CHOTMP), 35.9 (q, NC(*C*H$_3$)$_2$), 40.6 (t, NC*C*H$_2$CH$_2$CH$_2$CN), 40.7 (t, NCCH$_2$CH$_2$*C*H$_2$CN), 43.9 (t, CH*C*H$_2$CH), 50.3 (d, *C*HCH$_2$C≡), 51.0 (q, O*C*H$_3$), 55.0 (d, =CH*C*HCHOTBS), 59.3 (s, N*C*(CH$_3$)$_2$), 76.7 (d, *C*HOH), 77.2 (d, *C*HOTBS), 80.2 (s, *C*≡C), 80.53 (s, *C*≡C), 85.7 (d, *C*HOTMP), 128.7 (d, *C*H=CHCHOTMP), 136.6 (d, =*C*HCHOTMP), 172.9 (s, *C*OOMe).

Path V: Synthesis of 4-92 from 4-6b (see Scheme 4.36)

1,3-Dihydroxy-2-methylprop-2-yl 7-[*(1S*,2R*,3R*,5S*)*-3-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-2-[*(1E)*-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]oct-1-en-1-yl]cyclopentyl]hept-5-ynoate 4-93 and 1,3-dihydroxy-2-methylpropan-2-yl 7-[*(1S*,2R*,3R*,5S*)*-3,5-dihydroxy-2-[*(1E)*-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]oct-1-en-1-yl]cyclopentyl]hept-5-ynoate 4-94:



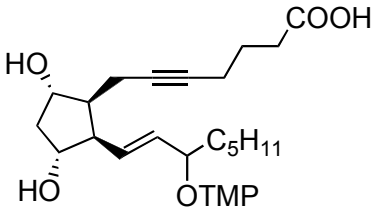
4-93



4-94

p-TsOH·H$_2$O (3.2 mg, 0.017 mmol, 0.6 equiv.) was added at r.t. to a solution of **4-6b** (15α/β aprox. 1:1.3, 22 mg, 0.027 mmol) in 4 mL MeOH and 0.2 mL water. The consumption was monitored by TLC with hexane/ethyl acetate 5:1 (R_f substrate = 0.63). After 24 h of stirring at r.t., a spatula tip of Na_2CO_3 was added and the reaction mixture was stirred for 10 min. The solvent was concentrated and the reaction mixture was partitioned between diethyl ether and water. The aqueous phase was extracted with diethyl ether. The combined ethereal phases were washed with brine and dried over Na_2SO_4. The solvent was evaporated to give 24 mg of crude **4-93** R_f(CH_2Cl_2/acetone 2:1) = 0.61. Crude **4-93** dissolved in 4 mL dry THF was treated at 0 °C with 0.135 mL (0.135 mmol) of a 1*M* TBAF solution in THF. The reaction mixture was stirred at 0 °C for 3 h and at r.t. for 30 min. The consumption was monitored by TLC with CH_2Cl_2/acetone 2:1. Then 0.07 mL of 1*M* TBAF solution in THF was added and stirred at r.t. for 10 min. It was quenched with 5 mL of saturated NH_4Cl solution and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether and once with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated to give 20 mg of crude **4-94**.

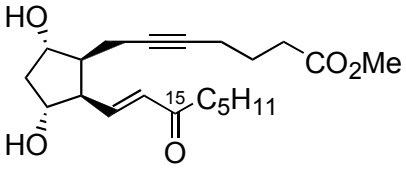
7-[*(1S*,2R*,3R*,5S*)*-3,5-Dihydroxy-2-[*(1E)*-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]oct-1-en-1-yl]cyclopentyl]hept-5-ynoic acid 4-95:



4-95

Crude **4-94** was dissolved in 3 mL THF and 0.5 mL water. $LiOH \cdot H_2O$ (43 mg, 1.02 mmol) was added at r.t. and the reaction mixture was stirred for 6.5 h. The reaction mixture was diluted with 10 mL diethyl ether and 3 mL of water. The aqueous layer was acidified with 20 mL of a 2*M* $NaHSO_4$ solution and extracted four times with diethyl ether. The ethereal layer was dried over Na_2SO_4 and concentrated in vacuo to give 9 mg of crude acids 15α/β-**4-95** (R_f(CH_2Cl_2/acetone 2:1) = 0.31, 0.37). The crude acids 15α/β-**4-95** were dissolved in 2 mL of dry THF and 0.2 mL of dry MeOH under a nitrogen atmosphere. To this solution 0.09 mL (0.18 mmol) of a 2*M* solution of $TMSCHN_2$ in diethyl ether was added and the reaction mixture was stirred at r.t. for 1 h and 20 min. The reaction mixture was evaporated to give the crude product. Purification by flash chromatography (CH_2Cl_2/acetone 10:1, gradient to 5:1, 2:1 and 1:1; the product eluted with 5:1) gave 6.5 mg (47% yield based on **4-6b**) of pure **4-92** as an inseparable mixture of 15α/15β-isomers. The diastereomeric ratio was 1.3:1, the relative configuration could however not be determined. R_f(ethyl acetate) = 0.53 and 0.60, R_f(CH_2Cl_2/acetone 2:1) = 0.53 and 0.62. Both isomers are well retained on silica and elute only in the presence of acetone.

5,6-Dehydro-15-oxo-F_{2t}-isoprostane 4-96:

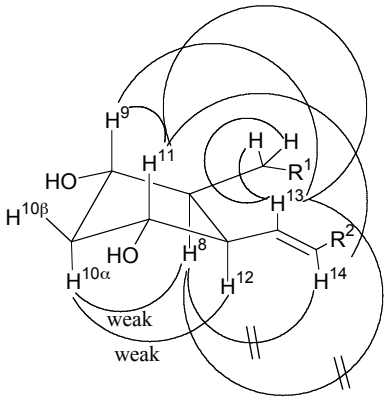


*m*CPBA (11.4 mg, 0.066 mmol, 1.4 equiv.) was added to a solution of **4-92** (17 mg, 0.033 mmol) in 3.5 mL of dry CH_2Cl_2 at 0 °C. The consumption was monitored by TLC with ethyl acetate (R_f(substrates) = 0.59, 0.67; R_f(product) = 0.39). The solution was stirred for 10 min at 0 °C, quenched with 5mL saturated $Na_2S_2O_3$ solution and diluted with ethyl acetate. The aqueous layer was extracted twice with diethyl ether and three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuum to give 50 mg of crude product. To avoid epimerisation, the product

was purified immediately. Flash chromatography (hexane/ethyl acetate 1:1 followed by ethyl acetate) gave 11.2 mg (93%) of pure **4-96**, R_f (ethyl acetate) = 0.39. The ketone **4-96** was reduced immediately or it was dried and stored in the freezer. Storage in solution for longer time leads to the formation of 12-*epi*-5,6-dehydro-15-oxo-F_{2t}-IsoP (**4-96**/12-*epi*-**4-96**>10:1).

^{1}H NMR (600 MHz, C_6D_6): δ = 0.86 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.23 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.30 (br. s, 2H, OH), 1.59 (m, 1H, $CHCH_2CH$), 1.66 (m, 4H, $CH_3(CH_2)_2CH_2$, CH_2CH_2COOMe), 1.89 (ddt, *J* = 16.7, 8.3, 2.5 Hz, 1H, $CHCH_2C{\equiv}$), 2.00 (m, 3H, ${\equiv}CCH_2CH_2$, $CHCH_2C{\equiv}$), 2.13 (quint, *J* = 7.0 Hz, 1H, $CHCH_2CH$), 2.23 (t, *J* = 7.3 Hz, 2H, CH_2COOMe), 2.27 (t, *J* = 7.3 Hz, 2H, $COCH_2CH_2$), 2.31 (m, 1H, $CHCH_2C{\equiv}$), 2.80 (m, 1H, $HOCHCHCH{=}$), 3.32 (s, 3H, OCH_3), 3.77 (dd, *J* = 11.3, 5.0 Hz, 1H, $HOCHCHCH{=}$), 3.89 (dt, *J* = 6.8, 4.8 Hz, 1H, $HOCHCHCH_2$), 6.10 (dd, *J* = 15.6, 0.7 Hz, 1H, $=CHCO$), 6.64 (dd, *J* = 15.6, 9.5 Hz, 1H, $CH{=}CHCO$). - ^{13}C NMR (150 MHz): δ = 14.2 (q, CH_2CH_3), 18.3 (t, $CH_2CH_2C{\equiv}$), 19.2 (t, $CHCH_2C{\equiv}$), 22.9 (t, CH_2CH_3), 24.0 (t, $CH_2CH_2CH_2CH_3$), 24.5 (t, $CH_2CH_2C{\equiv}$), 31.8 (t, $CH_2CH_2CH_3$), 32.8 (t, CH_2COOMe), 41.1 ($CHCOCH_2$), 43.0 (t, $CHCH_2CH$), 50.6 (d, $CHCH_2C{\equiv}$), 51.1 (q, OCH_3), 53.4 (d, $CHCHCH{=}$), 75.5 (d, $HOCHCHCH{=}$), 75.9 (d, $HOCHCHCH_2$), 79.9 (s, $C{\equiv}C$), 80.7 (s, $C{\equiv}C$), 132.0 (d, $=CHCO$), 143.4 (d, $CH{=}CHCO$), 173.2 (s, $COOMe$), 198.6 (s, CO). - IR (Film): $\tilde{\nu}$ = 3433 (br. w), 2923 (s), 2853 (s), 1737 (s), 1668 (m), 1625 (w), 1461 (w), 1438 (w), 1260 (w), 1080 (w), 1028 (w), 800 (w). - MS(ESI) *m/z* (%): 751 (17) [2M+Na$^+$], 387 (100) [M+Na$^+$]. - HRMS: $C_{21}H_{32}O_5Na^+$: calc. 387.2147; found 387.2136.

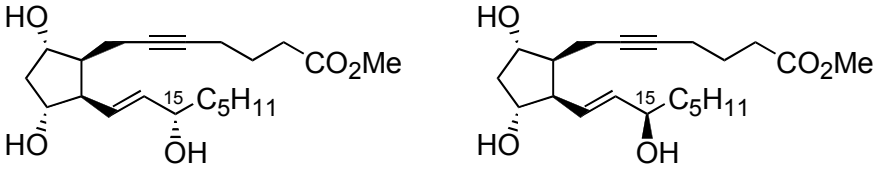
NOESY experiment of **4-96**:



12-*epi*-5,6-Dehydro-15-oxo-F_{2t}-isoprostane: This product was detected in the solution of 5,6-dehydro-15-oxo-F_{2t}-IsoP in small amounts. NOE Experiments for proving its stereochemistry were not possible. Based on the evidence, we assign it the 12-*epi* structure. Detectable resonances of this isomer are: ^{1}H NMR (600 MHz, C_6D_6): δ = 3.31 (s, 3H, OCH_3), 3.89 (m, 1H, $HOCHCHCH_2$), 4.01 (m, 1H, $HOCHCHCH{=}$), 6.12 (m, 1H, $=CHCO$), 6.64 (m,

1H, C*H*=CHCO). - ^{13}C NMR (150 MHz): δ = 40.09 (CHCO*C*H$_2$), 43.51 (t, CH*C*H$_2$CH), 53.32 (d, *C*HCH$_2$C≡), 76.12 (d, HO*C*HCHCH$_2$), 77.46 (d, HO*C*HCHCH=), 78.89 (s, *C*≡C), 80.87 (s, *C*≡C), 132.2 (d, =*C*HCO), 145.0 (d, *C*H=CHCO), 173.1 (s, *C*OOMe), 199.2 (s, CO).

5,6-Dehydro-15-F$_{2t}$-isoprostane methyl ester and 15-*epi*-5,6-dehydro-15-F$_{2t}$-isoprostane methyl ester 4-98:



A 1.7*M* solution of DIBAL-H (0.22 mL, 0.38 mmol, 12 equiv. based on **4-96**) in toluene was added to a solution of 111 mg (0.503 mmol, 1.32 equiv. based on DIBAL-H) of 2,6-di-*tert*-butyl-4-methylphenol in 1.3 mL of dry toluene at 0 °C and the solution was stirred for 1 h 15 min. After cooling to –95 °C, 11.2 mg (0.0307 mmol) **4-96** dissolved in 0.6 mL toluene was added to the colourless solution (reaching a reagent concentration of 0.2 M). A yellow to orange coloration was observed on addition of the substrate. The reaction mixture was warmed to –78 °C and stirred at this temperature for 2 h, then at –50 °C for 3 h, and finally it was allowed to warm up to –10 °C for 1 h 15 min, when it was complete by TLC (**4-96** R_f(ethyl acetate) = 0.39; 5,6-dehydro-15-F$_{2t}$-IsoP, R_f (ethyl acetate) = 0.15 (15-α) and 0.23 (15-β)). The reaction was quenched with 5 mL 1*M* HCl solution and diluted with ethyl acetate. The mixture was stirred for 5 min while allowed to warm up to room temperature. The aqueous layer was extracted four times with ethyl acetate and twice with diethyl ether. The combined etheral layers were washed with brine and dried over Na_2SO_4. Flash chromatography of the crude product (190 mg) was performed with hexane/ethyl acetate 1:1, followed by ethyl acetate and CH_2Cl_2/acetone 1:1. The products eluted with CH_2Cl_2/acetone 1:1 and a mixture of 5,6-dehydro-15-F$_{2t}$-IsoP and 15-*epi*-5,6-dehydro-15-F$_{2t}$-IsoP was isolated in 92% yield (10.4 mg) in a ratio of 1.7:1 (15-*epi*-5,6-dehydro-15-F$_{2t}$-IsoP R_f(CH_2Cl_2/acetone 2:1) = 0.23; 5,6-dehydro-15-F$_{2t}$-IsoP R_f(CH_2Cl_2/acetone 2:1) = 0.17). Although the R_f values of the products with ethyl acetate are 0.15 and 0.23, they elute only in the presence of acetone. At this stage, MS- and HRMS data were recorded. The products were separated by a second column using ethyl acetate/acetone 8:1 followed by 1:1 as the eluent. Three fractions were obtained: 2 mg of pure 15-*epi*-5,6-dehydro-15-F$_{2t}$-IsoP, 3.7 mg of a 1:1 mixture of 15-*epi*-5,6-dehydro-15-F$_{2t}$-IsoP and 5,6-dehydro-15-F$_{2t}$-IsoP, and finally 4.7 mg of pure 5,6-dehydro-15-F$_{2t}$-IsoP.

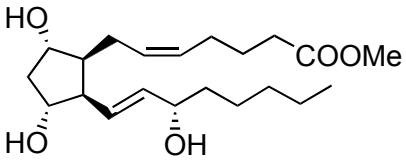
15α-/15β-**5,6-Dehydro-15-F$_{2t}$-IsoP:** IR (Film): $\tilde{\nu}$ = 3320 cm^{-1} (m), 2954 (m), 2928 (s), 2857 (m), 1739 (m), 1437 (m), 1249 (w), 1162 (w), 1162 (w), 1086 (w), 1060 (m), 971 (w). - MS(ESI) *m/z* (%): 389 (100) [M+Na$^+$]. - HRMS: $C_{21}H_{34}O_5Na^+$: calc. 389.2304; found 389.2305.

5,6-Dehydro-15-F$_{2t}$-IsoP: R_f(CH_2Cl_2/acetone 2:1) = 0.17. - ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H, CH_2CH_3), 1.20-1.35 (m, 5H, $CH_2CH_2CH_2CH_3$), 1.39 (m, 1H, $CH_2CH_2CH_2CH_3$), 1.47 (m, 1H, HOCHCH_2CH_2), 1.56 (m, 1H, HOCHCH_2CH_2), 1.65 (br. s, 2H, O*H*), 1.70 (dt, *J* = 14.2, 4.9 Hz, 1H, CHCH_2CH), 1.80 (quint, *J* = 7.1 Hz, 2H, CH_2CH_2COOMe), 2.05 (m, 1H, CHCH_2C≡), 2.19 (m, 1H, CHCH_2C≡), 2.22 (t, *J* = 7.0 Hz, 2H, ≡CCH_2CH_2), 2.32 (m, 2H, C*H*CH_2C≡, OH), 2.44 (t, *J* = 7.4 Hz, 2H, CH_2COOMe), 2.47 (m, 1H, CHCH_2CH), 2.78 (dt, *J* = 4.8, 8.9 Hz, 1H, HOCHC*H*CH=), 3.68 (s, 3H, OCH_3), 4.03 (q, *J* = 4.9 Hz, 1H, HOC*H*CHCH=), 4.06 (q, *J* = 6.3 Hz, 1H, =CHC*H*OH), 4.14 (dt, *J* = 7.0, 5.1 Hz, 1H, HOC*H*CHCH_2), 5.42 (dd, *J* = 15.3, 9.7 Hz, 1H, C*H*=CHCHOH), 5.59 (dd, *J* = 15.3, 6.9 Hz, 1H, =C*H*CHOH). - ^{13}C NMR (150 MHz): δ = 14.0 (q, CH_2CH_3), 18.1 (t, ≡CCH_2CH_2), 19.07 (t, CHCH_2C≡), 22.6 (t, CH_2CH_3), 24.1 (t, CH_2CH_2COOMe), 25.1 (t, $CH_2CH_2CH_2CH_3$), 31.7 (t, $CH_2CH_2CH_3$), 32.9 (t, CH_2COOMe), 37.29 (t, HOCHCH_2CH_2), 42.26 (t, CHCH_2CH), 49.69 (d, CHCH$_2$C≡), 51.7 (q, OCH_3), 53.4 (d, CH*C*HCH=), 72.61 (d, HO*C*HCH_2CH_2), 76.08 (d, HO*C*HCHCH=), 76.23 (d, HO*C*HCHCH_2), 79.87 (s, *C*≡C), 80.24 (s, *C*≡C), 128.3 (d, *C*H=CHCHOH), 136.62 (d, =*C*HCHOH), 173.81 (s, *C*OOMe).

15-*epi*-5,6-dehydro-15-F$_{2t}$-IsoP: R_f(CH_2Cl_2/acetone 2:1) = 0.23. - ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (m, 3H, CH_2CH_3), 1.20-1.35 (m, 5H, $CH_2CH_2CH_2CH_3$), 1.39 (m, 1H, $CH_2CH_2CH_2CH_3$), 1.48 (m, 1H, HOCHCH_2CH_2), 1.55 (m, 1H, HOCHCH_2CH_2), 1.61 (br. s, 3H, O*H*), 1.70 (dt, *J* = 14.3, 4.7 Hz, 1H, CHCH_2CH), 1.80 (quint, *J* = 7.0 Hz, 2H, CH_2CH_2COOMe), 2.07 (m, 1H, CHCH_2C≡), 2.22 (t, *J* = 6.7 Hz, 2H, ≡CCH_2CH_2), 2.23 (m, 1H, CHCH_2C≡), 2.34 (m, 1H, C*H*CH_2C≡), 2.44 (t, *J* = 7.3 Hz, 2H, CH_2COOMe), 2.47 (m, 1H, CHCH_2CH), 2.80 (dt, *J* = 4.5, 8.8 Hz, 1H, HOCHC*H*CH=), 3.68 (s, 3H, OCH_3), 4.03 (dd, *J* = 10.5, 4.6 Hz, 1H, HOC*H*CHCH=), 4.08 (q, *J* = 6.5 Hz, 1H, =CHC*H*OH), 4.15 (dt, *J* = 7.2, 4.9 Hz, 1H, HOC*H*CHCH_2), 5.44 (dd, *J* = 15.3, 9.5 Hz, 1H, C*H*=CHCHOH), 5.62 (dd, *J* = 15.4, 6.4 Hz, 1H, =C*H*CHOH). - ^{13}C NMR (150 MHz): δ = 14.0 (q, CH_2CH_3), 18.1 (t, ≡CCH_2CH_2), 19.11 (t, CHCH_2C≡), 22.6 (t, CH_2CH_3), 24.1 (t, CH_2CH_2COOMe), 25.1 (t, $CH_2CH_2CH_2CH_3$), 31.7 (t, $CH_2CH_2CH_3$), 32.9 (t, CH_2COOMe), 37.27 (t, HOCHCH_2CH_2), 42.23 (t, CHCH_2CH), 49.71 (d, CHCH$_2$C≡), 51.7 (q, OCH_3), 53.6 (d, CH*C*HCH=), 72.9 (d, HO*C*HCH_2CH_2), 76.06 (d, HO*C*HCHCH=), 76.21 (d, HO*C*HCHCH_2), 79.78 (s, *C*≡C), 80.24 (s, *C*≡C), 127.7 (d, *C*H=CHCHOH), 136.7 (d, =*C*HCHOH), 173.77 (s, *C*OOMe).

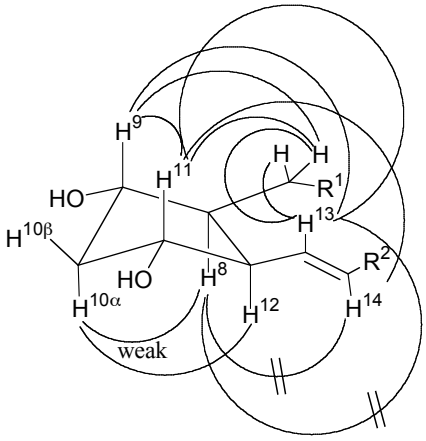
15-F_{2t}-IsoP 15α-4-1 and 15-*epi*-15-F_{2t}-IsoP 15β-4-1: In a Schlenk flask, 5 mg of the Lindlar catalyst (~5% Pd on calcium carbonate, poisoned with lead, FLUKA, filling code 1308421 11607082) was evacuated and flushed with nitrogen three times. In a separate Schlenk flask, a mixture of HPLC grade ethyl acetate/HPLC grade ethanol/distilled pyridine 11:6:1 was deoxygenated by five freeze-pump-thaw cycles and 3 mL of this solvent mixture was added to the catalyst. The suspension was subsequently evacuated and flushed three times with hydrogen and was then stirred under a positive pressure of H_2 at r.t. for 45 min. Hydrogenation was started by addition of a carefully deoxygenated solution of 5 mg (0.013 mmol) 5,6-dehydro-15-F_{2t}-IsoP or 15-*epi*-5,6-dehydro-15-F_{2t}-IsoP, respectively, in 1.5 mL of the same solvent mixture. The reaction mixture was stirred at r.t. for 24 hours under a slightly positive pressure of hydrogen (2 balloons). The reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite, which was washed with ethyl acetate and diethyl ether. The crude products were purified by flash chromatography on silica using first ethyl acetate to flush down unpolar impurities, followed by a gradient of ethyl acetate/acetone 10:1, and final product elution with ethyl acetate/acetone 3:1.

15-F_{2t}-IsoP methyl ester 15α-4-1: Yield 4.8 mg (96%) of pure F_{2t}-IsoP as a colourless oil, R_f(ethyl acetate) = 0.16. Only trace amounts, if at all of fully hydrogenated product were observed in the NMR spectra. The product matches the analytical data of the natural product.

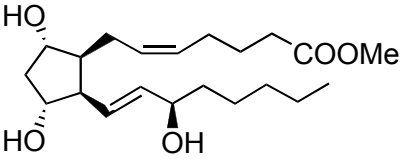


^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 1.24-1.42 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.48 (m, 1H, $HOCHCH_2CH_2$), 1.56 (m, 1H, $HOCHCH_2CH_2$), 1.67 (m, 3H, $HOCHCH_2CHOH$, CH_2CH_2COOMe), 2.01 (m, 5H, $CHCH_2CH$=, OH), 2.07 (q, *J* = 6.9 Hz, 2H, $=CHCH_2CH_2$), 2.18 (m, 1H, $CHCH_2C$=), 2.32 (t, *J* = 7.2 Hz, 2H, CH_2COOMe), 2.44 (dt, *J* = 14.6, 6.8 Hz, 1H, $HOCHCH_2CHOH$), 2.78 (dt, *J* = 8.6, 4.4 Hz, 1H, $HOCHCHCH$=), 3.68 (s, 3H, OCH_3), 3.98 (dt, *J* = 7.1, 4.5 Hz, 1H, $HOCHCHCH_2$), 4.05 (dt, *J* = 6.3, 4.2 Hz, 1H, $HOCHCHCH$=), 4.08 (q, *J* = 6.4 Hz, 1H, $=CHCHOH$), 5.43 (m, 3H, CH=$CHCHOH$, CH_2CH=$CHCH_2$), 5.59 (dd, *J* = 15.3, 6.7 Hz, 1H, $=CHCHOH$). - ^{13}C NMR (150 MHz): δ = 14.05 (q, CH_2CH_3), 22.62 (t, CH_2CH_3), 24.67 (t, CH_2CH_2COOMe), 25.16 (t, $CH_2CH_2CH_2CH_3$), 26.67 (t, $CH_2CH_2CH_2COOMe$), 26.98 (t, $CHCH_2CH$=), 31.72 (t, $CH_2CH_2CH_3$), 33.31 (t, CH_2COOMe), 37.24 (t, $HOCHCH_2CH_2$), 42.31 (t,

HOCH*C*H$_2$CHOH), 50.80 (d, *C*HCH$_2$CH=), 51.64 (q, O*C*H$_3$), 53.66 (d, CH*C*HCH=), 72.78 (d, HO*C*HCH$_2$CH$_2$), 76.46 (d, HO*C*HCHCH= or HO*C*HCHCH$_2$), 76.47 (d, HO*C*HCHCH= or HO*C*HCHCH$_2$), 128.81 (d, CH*C*H=CHCHOH), 129.17 (d, CHCH$_2$*C*H=CHCH$_2$ or CHCH$_2$CH=*C*HCH$_2$), 129.89 (d, CHCH$_2$*C*H=CHCH$_2$ or CHCH$_2$CH=*C*HCH$_2$), 136.20 (d, =*C*HCHOH), 174.25 (s, *C*OOMe). - IR (Film): $\tilde{\nu}$ = 3348 (br. m), 3006 (w), 2930 (s), 2859 (m), 1739 (s), 1438 (m), 1245 (w), 1169 (w), 1071 (m), 973 (m). - MS(ESI) *m/z* (%): 759 (5) [2M+Na$^+$], 391 (100) [M+Na$^+$]. - HRMS: $C_{23}H_{44}O_5Na^+$: calc. 391.2460; found 391.2466. - NOESY-correlations in 15α-**4-1:**



15-*epi*-15-F$_{2t}$-IsoP methyl ester 15β-4-1: Yield 4.9 mg (99%) as a colourless oil, R$_f$(ethyl acetate) = 0.22. Only trace amounts, if at all of fully hydrogenated product were observed in the NMR spectra. The analytical data of the synthesised product match those of the natural product.

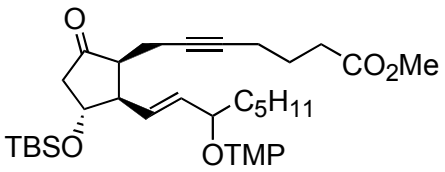


^{1}H NMR (600 MHz, CDCl$_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3H, CH$_2$C*H$_3$*), 1.25-1.42 (m, 6H, C*H$_2$*C*H$_2$*C*H$_2$*CH$_3$), 1.48 (m, 1H, HOCHC*H$_2$*CH$_2$), 1.55 (m, 1H, HOCHC*H$_2$*CH$_2$), 1.67 (m, 3H, HOCHC*H$_2$*CHOH, C*H$_2$*CH$_2$COOMe), 1.91 (br. s, 2H, O*H*), 1.96 (br. s, 1H, O*H*), 2.05 (q, *J* = 7.3 Hz, 2H, CHC*H$_2$*CH=), 2.07 (q, *J* = 7.4 Hz, 2H, =CHC*H$_2$*CH$_2$), 2.20 (m, 1H, C*H*CH$_2$CH=), 2.33 (t, *J* = 7.2 Hz, 2H, C*H$_2$*COOMe), 2.44 (ddd, *J* = 14.1, 7.4, 6.7 Hz, 1H, HOCHC*H$_2$*CHOH), 2.79 (ddd, *J* = 8.9, 8.2, 4.0 Hz, 1H, HOCHC*H*CH=), 3.68 (s, 3H, OC*H$_3$*), 4.00 (m, 1H, HOC*H*CHCH$_2$), 4.04 (ddd, *J* = 7.0, 4.0, 3.0 Hz, 1H, HOC*H*CHCH=), 4.09 (q, *J* = 6.3 Hz, 1H, =CHC*H*OH), 5.45 (m, 3H, C*H*=CHCHOH, CH$_2$C*H*=C*H*CH$_2$), 5.60 (dd, *J* = 15.3, 6.5 Hz, 1H, =C*H*CHOH). - ^{13}C NMR (150 MHz): δ = 14.06 (q, CH$_2$*C*H$_3$), 22.62 (t, *C*H$_2$CH$_3$), 24.62 (t, *C*H$_2$CH$_2$COOMe), 25.16 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 26.65 (t,

C$H_2CH_2CH_2COOMe$), 26.96 (t, CH*C*H_2CH=), 31.72 (t, *C*$H_2CH_2CH_3$), 33.23 (t, *C*H_2COOMe), 37.24 (t, HOCH*C*H_2CH_2), 42.34 (t, HOCH*C*H_2CHOH), 50.72 (d, *C*HCH_2CH=), 51.68 (q, O*C*H_3), 53.71 (d, CH*C*HCH=), 72.70 (d, HO*C*HCH_2CH_2), 76.54 (d, HO*C*HCHCH= or HO*C*$HCHCH_2$), 76.62 (d, HO*C*HCHCH= or HO*C*$HCHCH_2$), 128.43 (d, CH*C*H=CHCHOH), 129.26 (d, $CHCH_2$*C*H=$CHCH_2$ or $CHCH_2CH$=*C*HCH_2), 129.91 (d, $CHCH_2$*C*H=$CHCH_2$ or $CHCH_2CH$=*C*HCH_2), 136.29 (d, =*C*HCHOH), 174.34 (s, *C*OOMe).

6.9.7. Completion of the total syntheses of 13,14-dihydro-15-oxo-15-E_2-isoprostane 4-3 and 13,14-dihydro-15-oxoprostaglandin E_2 4-4

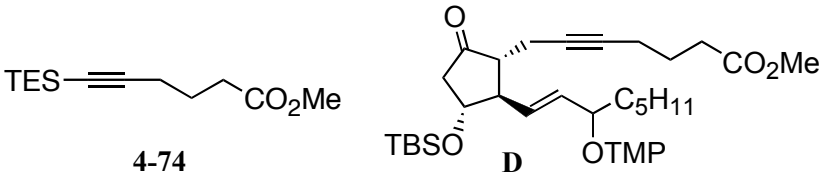
Methyl 7-[(1*S,2*R**,3*R**)-3-(*tert*-butyldimethylsilyloxy)-5-oxo-2-[(*R**,*E* *and* *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopent-1-yl]hept-5-ynoate 4-99:**



1. Tandem TES deprotection/Swern-type oxidation: A 2.0 *M* solution of oxalyl chloride in CH_2Cl_2 (0.43 mL, 0.86 mmol, 7 equiv.) was added at −70 °C to a solution of DMSO (0.122 mL, 1.72 mmol, 14 equiv.) in 2 mL dry CH_2Cl_2 and stirred for 40 min at this temperature. The mixture of **4-6a** (15α/β 1:1.6, 0.042 mmol), **4-9** (0.047 mmol) and **4-74** (0.034 mmol) (60 mg, 1.25:1.4:1) dissolved in 3 mL of dry CH_2Cl_2 was added at −70 °C. The reaction mixture was stirred at −70 - −40 °C for one hour and 40 min. It was cooled to −75 °C and Et_3N (0.48 mL, 3.44 mmol, 28 equiv.) was added. The consumption was followed by TLC (hexane/ethyl acetate 20:1 and 10:1; R_f(**4-6a**, hexane/ethyl acetate 20:1) = 0.4, R_f(aldehydes, hexane/ethyl acetate 10:1) = 0.30-0.45). The reaction was stirred at −40 - 0 °C for 2.5 h and quenched with 5 mL water. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was suspended in diethyl ether and separated from a colourless solid to give 100 mg of a pale yellow oil. The reaction was similarly repeated with further 30 mg of the same mixture of 15α,β-**4-6a**, **4-9** and **4-74**. The combined crude products from both experiments (total 130 mg) were used immediately for the next step.

2. Aldehyde to acid oxidation and esterification to 4-99: The crude mixture of aldehydes (130 mg) was dissolved in 4.2 mL of a 2:1 *t*BuOH/H_2O mixture. NaH_2PO_4 (104.4 mg, 0.87 mmol, 4.7 equiv.) dissolved in a small amount of water and 2-methyl-2-butene (0.184 mL, 1.74 mmol, 9.4 equiv.) were added to this solution. $NaClO_2$ (79 mg, 0.87 mmol, 4.7 equiv.)

was added in one portion at 0 °C and the reaction was stirred at r.t. for 2 h. The consumption of the aldehydes was followed by TLC (hexane/ethyl acetate 10:1). The reaction mixture was quenched with 4 mL of a 5% HCl solution. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The mixture of crude acids (100 mg) was dissolved in 5.6 mL of a dry 8.5:1 THF/MeOH mixture. Trimethylsilyldiazomethane (0.725 mL, 1.45 mmol, 2.0 *M* in Et_2O, 7.9 equiv.) was added and the reaction mixture was stirred at r.t. for 3 h. The formation of the methyl esters was followed by TLC (hexane/ethyl acetate 5:1: R_f(products 5:1) = 0.54). The solvent was evaporated to give 100 mg of crude esters. Flash chromatography (hexane/ethyl acetate 40:1, gradient to 2:1) gave first 20 mg of TES-alkyne methyl ester **C** (hexane/ethyl acetate 40-20:1), 5 mg of a 15β-**4-99**/PG isomer **D** mixture (5.25:1) (with hexane/ethyl acetate 10:1) and 23 mg of **4-99** (15β/α = 1.4:1) (with hexane/ethyl acetate 5:1). Yield 28 mg (72%) from 15α/β-**4-6a** in an overall 15β/α-ratio of 1.8:1 and a **4-99**:**D** ratio of 34:1. Epimerisation to isomer **D** with PG configuration occurred thus only to a very small extent at this stage.

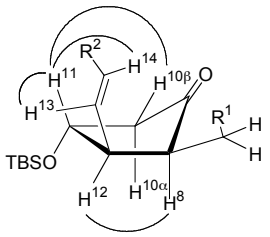


4-74 **D**

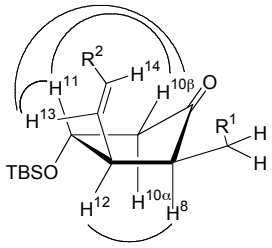
IR (Film): $\tilde{\nu}$ = 2953 (s), 2931 (s), 2858 (m), 1745 (s), 1466 (w), 1437 (w), 1375 (w), 1361 (w), 1255 (w), 1133 (w), 1077 (w), 1006 (w), 975 (w), 909 (w), 836 (m), 778 (m) cm^{-1}. - MS(ESI) *m/z* (%): 640 (100) [M+Na^+], 618 (16) [M+H^+], 484 (52) [M+H^+–TEMPO], 158 (26) [$TEMPOH_2^+$]. - HRMS: $C_{36}H_{63}NO_5SiNa^+$: calc. 640.4373; found 640.4371.

15β-**4-99**: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.07 (s, 3H, Si(C*H*$_3$)$_2$), 0.92 (m, 12H, CH_2CH_3, SiC(C*H*$_3$)$_3$), 1.14-1.52 (m, 12H, $CH_2CH_2CH_2CH_2CH_3$, NCC*H*$_2$C*H*$_2$C*H*$_2$CN), 1.21 (s, 3H, NC(C*H*$_3$)$_2$), 1.23 (s, 3H, NC(C*H*$_3$)$_2$), 1.26 (s, 3H, NC(C*H*$_3$)$_2$), 1.27 (s, 3H, NC(C*H*$_3$)$_2$), 1.57 (m, 1H, C*H*$_2$CHOTMP), 1.68 (m, 2H, C*H*$_2$CH$_2$COOMe), 1.84 (m, 1H, C*H*$_2$CHOTMP), 2.02 (m, 2H, ≡CC*H*$_2$CH$_2$), 2.20 (m, 1H, COC*H*$_2$CHO), 2.25 (t, *J* = 7.4 Hz, 2H, C*H*$_2$COOMe), 2.35 (dd, *J* = 18.7, 5.7 Hz, 1H, COC*H*$_2$CHO), 2.41 (ddt, *J* = 16.7, 9.5, 2.4 Hz, 1H, CHC*H*$_2$C≡), 2.88 (ddt, *J* = 16.6, 3.8, 2.3 Hz, 1H, CHC*H*$_2$C≡), 2.95 (dt, *J* = 3.6, 8.9 Hz, 1H, C*H*CH$_2$C≡), 3.16 (br. t, *J* = 8.6 Hz, 1H, CHC*H*CH=), 3.33 (s, 3H, COOC*H*$_3$), 4.25 (m, 1H, C*H*OTMP), 4.33 (dt, *J* = 2.7, 5.5 Hz, 1H, C*H*OTBS), 5.30 (dd, *J* = 15.4, 9.3 Hz, 1H, C*H*=CHCHOTMP), 5.72 (dd, *J* = 15.4, 8.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz, C_6D_6): δ = –4.75 (q, Si(*C*H$_3$)$_2$), –4.71 (q, Si(*C*H$_3$)$_2$), 14.27 (q, CH$_2$*C*H$_3$), 16.0 (t, CH*C*H$_2$C≡), 17.69 (t, NCCH$_2$*C*H$_2$CH$_2$CN), 18.23 (s,

Si*C*$(CH_3)_3$), 18.4 (t, $CH_2CH_2C{\equiv}$), 20.6 (q, NC(CH_3)$_2$), 20.73 (q, NC(CH_3)$_2$), 23.07 (t, CH_2CH_3), 24.50 (t, CH_2CH_2COOMe), 25.7 (t, $CH_2CH_2CH_2CH_3$), 25.96 (q, SiC(CH_3)$_3$), 32.3 (t, $CH_2CH_2CH_3$), 32.82 (t, CH_2COOMe), 34.5 (q, NC(CH_3)$_2$), 34.9 (t, $CH_2CHOTMP$), 35.3 (q, NC(CH_3)$_2$), 40.4 (t, $NCCH_2CH_2CH_2CN$), 40.6 (t, $NCCH_2CH_2CH_2CN$), 46.1 (t, $COCH_2CHO$), 50.8 (d, $CHCH_2C{\equiv}$), 50.99 (q, $COOCH_3$), 52.1 (d, $CHCHCH{=}$), 59.4 (s, NC(CH_3)$_2$), 60.5 (s, NC(CH_3)$_2$), 73.1 (d, *C*HOTBS), 79.6 (s, *C*≡C), 80.3 (s, *C*≡C), 85.2 (d, *C*HOTMP), 128.6 (d, *C*H=CHCHOTMP), 137.5 (d, =*C*HCHOTMP), 172.9 (s, *C*OOMe), 213.6 (s, *C*=O). - Significant NOESY interactions:

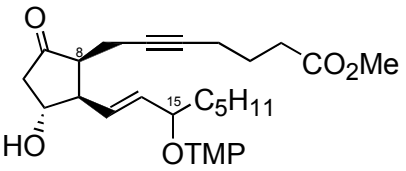


15α-**4-99**: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.08 (s, 3H, Si(C*H*$_3$)$_2$), 0.89 (m, 12H, CH_2CH_3, SiC(C*H*$_3$)$_3$), 1.11-1.51 (m, 12H, $CH_2CH_2CH_2CH_2CH_3$, $NCCH_2CH_2CH_2CN$), 1.18 (s, 3H, NC(C*H*$_3$)$_2$), 1.22 (s, 3H, NC(C*H*$_3$)$_2$), 1.26 (s, 3H, NC(C*H*$_3$)$_2$), 1.28 (s, 3H, NC(C*H*$_3$)$_2$), 1.56 (m, 1H, $CH_2CHOTMP$), 1.66 (m, 2H, CH_2CH_2COOMe), 1.88 (m, 1H, $CH_2CHOTMP$), 2.01 (m, 2H, $\equiv CCH_2CH_2$), 2.08 (m, 3H, $COCH_2CHO$, $CHCH_2C{\equiv}$), 2.23 (t, *J* = 7.7 Hz, 2H, CH_2COOMe), 2.82 (m, 1H, $CHCH_2C{\equiv}$), 2.98 (ddd, *J* = 3.9, 7.6, 11.3 Hz, 1H, $CHCH_2C{\equiv}$), 3.22 (m, 1H, $CHCHCH{=}$), 3.33 (s, 3H, $COOCH_3$), 4.13 (dt, *J* = 4.6, 8.9 Hz, 1H, C*H*OTMP), 4.25 (m, 1H, C*H*OTBS), 4.96 (dd, *J* = 15.1, 10.4 Hz, 1H, C*H*=CHCHOTMP), 5.75 (dd, *J* = 15.2, 9.0 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz, C_6D_6): δ = –4.81 (q, Si(CH_3)$_2$), –4.68 (q, Si(CH_3)$_2$), 14.34 (q, CH_2CH_3), 15.9 (t, $CHCH_2C{\equiv}$), 17.68 (t, $NCCH_2CH_2CH_2CN$), 18.23 (s, Si*C*$(CH_3)_3$), 18.3 (t, $CH_2CH_2C{\equiv}$), 20.4 (q, NC(CH_3)$_2$), 20.73 (q, NC(CH_3)$_2$), 23.14 (t, CH_2CH_3), 24.54 (t, CH_2CH_2COOMe), 25.6 (t, $CH_2CH_2CH_2CH_3$), 25.98 (q, SiC(CH_3)$_3$), 32.4 (t, $CH_2CH_2CH_3$), 32.78 (t, CH_2COOMe), 34.2 (q, NC(CH_3)$_2$), 35.0 (t, $CH_2CHOTMP$), 36.2 (q, NC(CH_3)$_2$), 40.5 (t, $NCCH_2CH_2CH_2CN$), 40.7 (t, $NCCH_2CH_2CH_2CN$), 45.6 (t, $COCH_2CHO$), 49.9 (d, $CHCH_2C{\equiv}$), 51.01 (q, $COOCH_3$), 52.9 (d, $CHCHCH{=}$), 59.2 (s, NC(CH_3)$_2$), 60.6 (s, NC(CH_3)$_2$), 72.6 (d, *C*HOTBS), 79.1 (s, *C*≡C), 80.0 (s, *C*≡C), 85.8 (d, *C*HOTMP), 127.2 (d, *C*H=CHCHOTMP), 138.6 (d, =*C*HCHOTMP), 172.8 (s, *C*OOMe), 213.9 (s, *C*=O). - Significant NOESY interactions:



PG-Isomer **D**, detectable resonances: ^{1}H NMR (600 MHz, C_6D_6): δ = 2.20 (m, 1H, COC*H*$_2$CHO), 2.56 (m, 1H, COC*H*$_2$CHO), 3.77 (br. d, *J* = 6.8 Hz, 1H, CHC*H*CH=), 4.25 (m, 2H, C*H*OTBS, C*H*OTMP), 5.61 (dd, *J* = 15.5, 6.8 Hz, 1H, C*H*=CHCHOTMP), 5.66 (dd, *J* = 15.4, 8.3 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz, C_6D_6): δ = 47.3 (t, CO*C*H$_2$CHO), 57.8 (d, CH*C*HCH=), 78.5 (d, *C*HOTBS), 85.8 (d, *C*HOTMP), 130.0 (d, *C*H=*C*HCHOTMP).

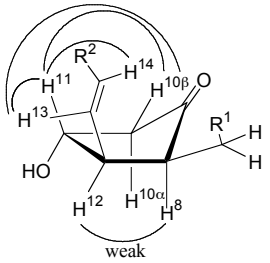
Methyl 7-[(1*S,2*R**,3*R**)-3-hydroxy-5-oxo-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentyl]hept-5-ynoate 4-100a:**



40% HF (0.11 mL, 2.5 mmol, 9.2 equiv. based on pyridine) was added to a solution of pyridine (0.022 mL, 0.272 mmol, 8.5 equiv. based on 15α/β-**4-99**) in 1.5 mL CH_3CN at 0 °C. A solution of pure **4-99** (15β/α 1.4:1, 20 mg, 0.032 mmol)) dissolved in 1 mL acetonitrile was added at 0 °C to this solution and the flask was rinsed with 1 mL acetonitrile. The reaction mixture was allowed to warm to room temperature and stirred until complete by TLC (R_f(**4-99**, hexane/ethyl acetate 5:1) = 0.56; R_f(**4-100a**-Isomer I, hexane/ethyl acetate 2:1) = 0.48; R_f(**4-100a**-Isomer II, hexane/ethyl acetate 2:1) = 0.57). After 19 h, the reaction was quenched with sat'd $NaHCO_3$ solution and diluted with CH_2Cl_2. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product (18.7 mg) was purified by flash chromatography (hexane/ethyl acetate 4:1, gradient to 2:1, and finally to ethyl acetate). Product 15α/β-**4-100a** eluted with hexane/ethyl acetate 2:1. Yield 10.2 mg (63%) with a **4-100a**:**4-100b** ratio of >9:1. Compound **4-100a** was isolated as a 1:1 mixture of the 15α/β-diastereomers. The sterochemistry at the 15-position could however not be assigned.

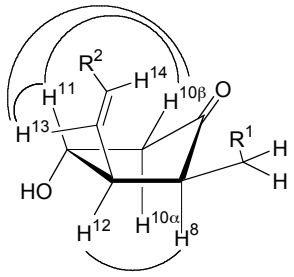
IR (Film): $\tilde{\nu}$ = 3475 (br. w), 2931 (s), 2871 (w), 1742 (s), 1459 (w), 1437 (w), 1376 (w), 1240 (w), 1162 (w), 1134 (w), 975 (w) cm^{-1}. - MS(ESI) *m/z* (%): 1029 (20) [2M+Na$^+$], 526 (100) [M+Na$^+$], 370 (39) [M+Na$^+$–TEMPO]. - HRMS: $C_{30}H_{49}NO_5Na^+$: calc. 526.3508; found 526.3506.

4-100a-Isomer I: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.73 (br. s, 1H, O*H*), 0.91 (m, 3H, CH_2CH_3), 1.11-1.44 (m, 21H, $CH_2CH_2CH_2CH_2CH_3$, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$), 1.48-1.62 (m, 4H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$), 1.66 (m, 2H, CH_2CH_2COOMe), 1.83 (m, 1H, $CH_2CHOTMP$), 1.95-2.09 (m, 3H, $\equiv CCH_2CH_2$, $COCH_2CHO$), 2.12-2.28 (m, 3H, $COCH_2CHO$, CH_2COOMe), 2.37 (m, 1H, $CHCH_2C\equiv$), 2.79 (m, 1H, $CHCH_2C\equiv$), 2.87 (m, 1H, $CHCH_2C\equiv$), 2.93 (m, 1H, $CHCHCH=$), 3.31 (s, 3H, $COOCH_3$), 4.03 (m, 1H, C*H*OH), 4.19 (m, 1H, C*H*OTMP), 5.17 (dd, *J* = 15.4, 9.2 Hz, 1H, C*H*=CHCHOTMP), 5.65 (dd, *J* = 15.4, 8.8 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.31 (q, CH_2CH_3), 15.9 (t, $CHCH_2C\equiv$), 17.7 (t, $NCCH_2CH_2CH_2CN$), 18.5 (t, $CH_2CH_2C\equiv$), 20.6 (q, $NC(CH_3)_2$), 20.7 (q, $NC(CH_3)_2$), 23.09 (t, CH_2CH_3), 24.48 (t, CH_2CH_2COOMe), 25.7 (t, $CH_2CH_2CH_2CH_3$), 32.3 (t, $CH_2CH_2CH_3$), 32.85 (t, CH_2COOMe), 34.5 (q, $NC(CH_3)_2$), 35.0 (t, $CH_2CHOTMP$), 35.2 (q, $NC(CH_3)_2$), 40.5 (t, $NCCH_2CH_2CH_2CN$), 40.6 (t, $NCCH_2CH_2CH_2CN$), 45.1 (t, $COCH_2CHO$), 50.7 (d, $CHCH_2C\equiv$), 51.06 (q, $COOCH_3$), 51.4 (d, $CHCHCH=$), 59.4 (s, $NC(CH_3)_2$), 60.6 (s, $NC(CH_3)_2$), 71.9 (d, *C*HOH), 79.7 (s, *C*≡C), 80.22 (s, *C*≡C), 85.2 (d, *C*HOTMP), 128.3 (d, *C*H=CHCHOTMP), 137.5 (d, =*C*HCHOTMP), 173.1 (s, *C*OOMe), 213.6 (s, *C*=O). - Significant NOESY interactions:

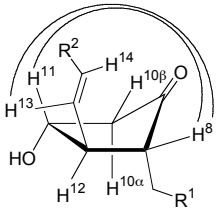


4-100a-Isomer II: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.73 (br. s, 1H, O*H*), 0.91 (m, 3H, CH_2CH_3), 1.11-1.44 (m, 21H, $CH_2CH_2CH_2CH_2CH_3$, $NCCH_2CH_2CH_2CN$, $NC(CH_3)_2$), 1.48-1.62 (m, 4H, $NCCH_2CH_2CH_2CN$, $CH_2CHOTMP$), 1.66 (m, 2H, CH_2CH_2COOMe), 1.83 (m, 1H, $CH_2CHOTMP$), 1.95-2.09 (m, 3H, $\equiv CCH_2CH_2$, $COCH_2CHO$), 2.12-2.28 (m, 4H, $COCH_2CHO$, CH_2COOMe, $CHCH_2C\equiv$), 2.70 (m, 1H, $CHCH_2C\equiv$), 2.79 (m, 1H, $CHCH_2C\equiv$), 2.93 (m, 1H, $CHCHCH=$), 3.33 (s, 3H, $COOCH_3$), 4.09 (m, 1H, C*H*OH), 4.19 (m, 1H, C*H*OTMP), 5.13 (dd, *J* = 15.2, 10.0 Hz, 1H, C*H*=CHCHOTMP), 5.69 (dd, *J* = 15.2, 8.9 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.35 (q, CH_2CH_3), 16.1 (t, $CHCH_2C\equiv$), 17.6 (t, $NCCH_2CH_2CH_2CN$), 18.3 (t, $CH_2CH_2C\equiv$), 20.5 (q, $NC(CH_3)_2$), 20.7 (q, $NC(CH_3)_2$), 23.13 (t, CH_2CH_3), 24.49 (t, CH_2CH_2COOMe), 25.6 (t, $CH_2CH_2CH_2CH_3$), 32.4 (t, $CH_2CH_2CH_3$), 32.81 (t, CH_2COOMe), 34.2 (q, $NC(CH_3)_2$), 35.1 (t, $CH_2CHOTMP$), 35.7 (q, $NC(CH_3)_2$), 40.4 (t, $NCCH_2CH_2CH_2CN$), 40.5 (t, $NCCH_2CH_2CH_2CN$), 45.0 (t, $COCH_2CHO$), 49.9 (d, $CHCH_2C\equiv$), 51.07 (q, $COOCH_3$), 52.1 (d, $CHCHCH=$), 59.3 (s,

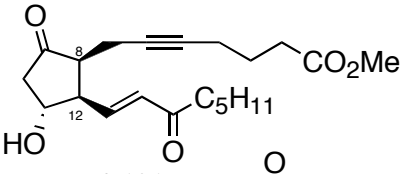
N*C*(CH_3)$_2$), 60.4 (s, N*C*(CH_3)$_2$), 71.6 (d, *C*HOH), 79.1 (s, *C*≡C), 80.21 (s, *C*≡C), 85.6 (d, *C*HOTMP), 127.8 (d, *C*H=CHCHOTMP), 137.9 (d, =*C*HCHOTMP), 173.0 (s, *C*OOMe), 213.9 (s, *C*=O). - Significant NOESY interactions:



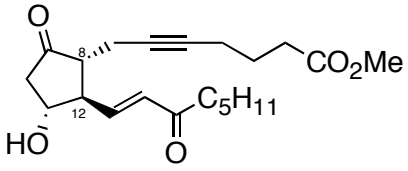
4-100b - detectable resonances: ^{1}H NMR (600 MHz, C_6D_6): δ = 1.63 (m, 1H, C*H*CH_2C≡), 2.13 (m, 1H, COC*H*$_2$CHO), 2.45 (m, 1H, COC*H*$_2$CHO), 2.85 (m, 1H, CHC*H*CH=), 3.28 (s, 3H, COOC*H*$_3$), 3.59 (m, 1H, C*H*OH), 4.25 (m, 1H, C*H*OTMP), 5.24 (dd, *J* = 15.4, 8.3 Hz, 1H, C*H*=CHCHOTMP), 5.73 (dd, *J* = 15.4, 9.0 Hz, 1H, =C*H*CHOTMP). - ^{13}C NMR (150 MHz, C_6D_6): δ = 47.0 (t, CO*C*H_2CHO), 51.10 (q, COO*C*H_3), 52.5 (d, CH*C*HCH=), 53.6 (d, *C*HCH$_2$C≡), 72.1 (d, *C*HOH), 78.1 (s, *C*≡C), 81.4 (s, *C*≡C), 85.5 (d, *C*HOTMP), 131.0 (d, *C*H=CHCHOTMP), 137.2 (d, =*C*HCHOTMP), 173.2 (s, *C*OOMe), 211.3 (s, *C*=O). - Significant NOESY interactions:



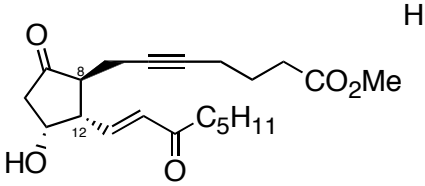
Methyl 7-[(1*S,2*R**,3*R**)-3-hydroxy-5-oxo-2-[(*E*)-3-oxooct-1-enyl]cyclopentyl]hept-5-ynoate 4-101a, methyl 7-[(1*R**,2*R**,3*R**)-3-hydroxy-5-oxo-2-[(*E*)-3-oxooct-1-enyl]cyclopentyl]hept-5-ynoate 4-101b and methyl 7-[(1*S**,2*S**,3*R**)-3-hydroxy-5-oxo-2-[(*E*)-3-oxooct-1-enyl]cyclopentyl]hept-5-ynoate 4-101c:**



4-101a



4-101b



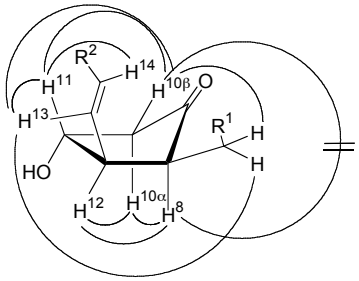
4-101c

*m*CPBA (70%, 10 mg, 0.04 mmol, 2 equiv.) was added to a solution of 10 mg of ketone 15α,β-**4-100a** and **4-100b** (0.02 mmol, 9:1) in 3 mL dry CH_2Cl_2 at 0 °C. The reaction was

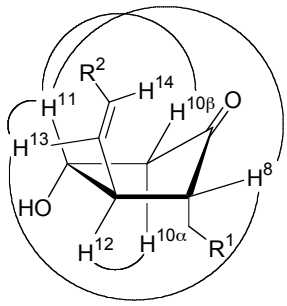
monitored by TLC (hexane/ethyl acetate 2:1: R_f(**4-100a**-major) = 0.48, R_f(**4-100a**-minor) = 0.57, R_f(**4-101a/4-101b/4-101c**) = 0.19 and R_f(*m*CPBA) = 0.69). After 13 min, the reaction was quenched with 5 mL concentrated $Na_2S_2O_3$ solution, diluted with ethyl acetate and stirred at r.t. for 10 min. The aqueous layer was extracted three times with ethyl acetate and three times with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified on a short column with hexane/ethyl acetate 5:1, gradient to ethyl acetate. The product **4-101a** contaminated with *m*-chlorobenzoic acid (total 10 mg) eluted with hexane/ethyl acetate 1:1 (R_f = 0.39) and ethyl acetate. A second purification with hexane/ethyl acetate 2:1 and 1:1 gave 5.4 mg (75% yield) of an inseparable mixture of **4-101a**, **4-101b** and **4-101c** in a ratio of IsoP:PG:12-*epi*-IsoP = 9:4:1.

IR (Film): $\tilde{\nu}$ = 3463 (br. w), 2954 (w), 2931 (w), 2870 (w), 1740 (s), 1669 (m), 1628 (w), 1436 (w), 1373 (w), 1341 (w), 1319 (w), 1226 (w), 1161 (m), 1079 (w), 984 (w) cm^{-1}. - MS(ESI) *m/z* (%): 747 (15) [2M+Na^+], 385 (100) [M+Na^+]. - HRMS: $C_{21}H_{30}O_5Na^+$: calc. 385.1991; found 385.1988.

4-101a: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.86 (m, 3H, CH_2CH_3), 1.13-1.26 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.32 (m, 1H, O*H*), 1.53-1.68 (m, 4H, CH_2CH_2COOMe, CH_2CH_2CO), 1.92-1.98 (m, 3H, $COCH_2CHO$, $\equiv CCH_2CH_2$), 2.01-2.16 (m, 2H, $CHCH_2C\equiv$, $COCH_2CHO$), 2.20 (t, *J* = 7.4 Hz, 2H, CH_2CH_2CO), 2.26 (t, *J* = 7.4 Hz, 2H, CH_2COOMe), 2.48 (ddt, *J* = 17.0, 4.4, 2.3 Hz, 1H, $CHCH_2C\equiv$), 2.68 (dt, *J* = 4.1, 8.9 Hz, 1H, $CHCH_2C\equiv$), 2.84 (ddd, *J* = 11.5, 8.3, 3.2 Hz, 1H, CHCHCH=), 3.31 (s, 3H, $COOCH_3$), 3.86 (dt, *J* = 5.9, 3.1 Hz, 1H, CHOH), 6.18 (dd, *J* = 15.6, 0.6 Hz, 1H, =CHCO), 6.54 (dd, *J* = 15.6, 9.9 Hz, 1H, CH=CHCO). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.2 (q, CH_2CH_3), 16.3 (t, $CHCH_2C\equiv$), 18.4 (t, $CH_2CH_2C\equiv$), 23.0 (t, CH_2CH_3), 24.1 (t, CH_2CH_2COOMe or $CH_2CH_2CH_2CH_3$), 24.5 (t, CH_2CH_2COOMe or $CH_2CH_2CH_2CH_3$), 31.8 (t, $CH_2CH_2CH_3$), 32.9 (t, CH_2COOMe), 41.0 (t, $CH_2CH_2C=O$), 45.4 (t, $COCH_2CHO$), 50.2 (d, $CHCH_2C\equiv$), 51.18 (q, $COOCH_3$), 51.5 (d, CHCHCH=), 71.2 (d, CHOH), 78.7 (s, C≡C), 81.0 (s, C≡C), 133.3 (d, =CHCO), 140.8 (d, CH=CHCO), 173.1 (s, COOMe), 198.4 (s, =CHC=O), 212.8 (s, C=O). - Significant NOESY-Cross-Peaks:

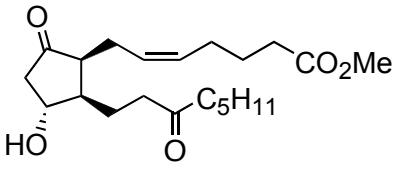


4-101b: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.86 (m, 3H, CH_2CH_3), 0.96 (br. s, 1H, O*H*), 1.13-1.26 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.53-1.68 (m, 5H, CH_2CH_2COOMe, CH_2CH_2CO, $CHCH_2C\equiv$), 1.92-1.98 (m, 2H, $\equiv CCH_2CH_2$), 2.01-2.16 (m, 2H, $CHCH_2C\equiv$, $COCH_2CHO$), 2.17 (t, *J* = 7.3 Hz, 2H, CH_2CH_2CO), 2.24 (t, *J* = 7.4 Hz, 2H, CH_2COOMe), 2.37 (dd, *J* = 18.3, 7.5 Hz, 1H, $COCH_2CHO$), 2.58 (ddt, *J* = 17.0, 4.9, 2.4 Hz, 1H, $CHCH_2C\equiv$), 2.78 (dt, *J* = 11.8, 8.7 Hz, 1H, $CHCHCH=$), 3.28 (s, 3H, $COOCH_3$), 3.48 (m, 1H, C*H*OH), 6.24 (dd, *J* = 15.6, 0.7 Hz, 1H, =C*H*CO), 6.63 (dd, *J* = 15.6, 8.5 Hz, 1H, C*H*=CHCO). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.2 (q, CH_2CH_3), 17.3 (t, $CHCH_2C\equiv$), 18.2 (t, $CH_2CH_2C\equiv$), 23.0 (t, CH_2CH_3), 24.0 (t, CH_2CH_2COOMe or $CH_2CH_2CH_2CH_3$), 24.4 (t, CH_2CH_2COOMe or $CH_2CH_2CH_2CH_3$), 31.9 (t, $CH_2CH_2CH_3$), 32.9 (t, CH_2COOMe), 41.4 (t, CH_2CH_2CO), 46.7 (t, $COCH_2CH$), 51.22 (q, $COOCH_3$), 52.6 (d, $CHCHCH=$), 53.1 (d, $CHCH_2C\equiv$), 71.6 (d, *C*HOH), 77.8 (s, *C*≡C), 81.9 (s, *C*≡C), 132.2 (d, =*C*HCO), 144.2 (d, *C*H=CHCO), 173.3 (s, *C*OOMe), 198.4 (s, =CH*C*=O), 210.3 (s, *C*=O). - Significant NOESY cross peaks:

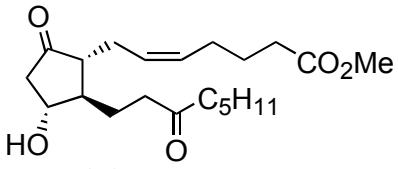


4-101c (12-*epi*-IsoP Isomer, detectable resonances): ^{1}H NMR (600 MHz, C_6D_6): 2.01-2.16 (m, 3H, $CHCH_2C\equiv$, $COCH_2CHO$), 2.25 (m, 1H, $CHCH_2C\equiv$), 2.64 (ddt, *J* = 16.9, 4.5, 2.3 Hz, 1H, $CHCH_2C\equiv$), 2.73 (ddd, *J* = 12.0, 8.7, 3.7 Hz, 1H, $CHCHCH=$), 3.30 (s, 3H, $COOCH_3$), 3.79 (t, *J* = 4.1 Hz, 1H, C*H*OH), 6.91 (dd, *J* = 16.0, 8.5 Hz, 1H, C*H*=CHCO).

13,14-Dihydro-15-oxo-15-E$_2$-IsoP methyl ester 4-3 and 13,14-dihydro-15-oxo-PGE$_2$ methyl ester 4-4:



4-3



4-4

In a Schlenk flask 5 mg of the Lindlar catalyst (~5% Pd on calcium carbonate, poisoned with lead, FLUKA, filling code 1308421 11607082) was evacuated and flushed with nitrogen three times. In a separate Schlenk flask, a 10:6:1 mixture of HPLC grade ethyl acetate/HPLC grade ethanol/distilled pyridine was deoxygenated by five freeze-pump-thaw cycles and 2 mL of

this solvent mixture was added to the catalyst. The suspension was subsequently evacuated and flushed three times with hydrogen and stirred under a positive pressure of H_2 at r.t. for 50 min. Hydrogenation was started by addition of a carefully deoxygenated solution of 5 mg (0.014 mmol) 15-oxo-5,6-dehydro-E_2-IsoP, 15-oxo-5,6-dehydro-PGE and 12-*epi*-15-oxo-5,6-dehydro-E_2-IsoP **4-101a/4-101b/4-101c** (9:4:1) in 1.7 mL of the same solvent mixture. The reaction mixture was stirred at r.t. for 24 hours under a slightly positive pressure of hydrogen (2 balloons of 26 cm diameter). The reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite, which was washed with ethyl acetate and diethyl ether. The crude product was purified by flash chromatography (hexane/ethyl acetate 5:1, gradient to ethyl acetate). The products **4-3** and **4-4** were obtained as a partly separable mixture with hexane/ethyl acetate 1:1 and ethyl acetate (R_f(hexane/ethyl acetate 1:1) = 0.23, 0.30). Yield 4.6 mg (90%) in a ratio of 1.5:1.

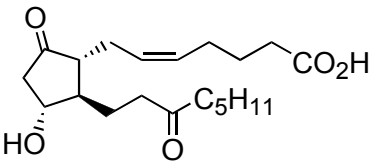
IR (Film): $\tilde{\nu}$ = 3464 (br. w), 3007 (w), 2953 (w), 2931 (w), 2869 (w), 1738 (s), 1715 (m), 1438 (w), 1372 (w), 1243 (w), 1163 (w), 1079 (w), 1016 (w) cm^{-1}. - MS (ESI) *m/z* (%): 389 (100) [$M+Na^+$]. - HRMS: $C_{21}H_{34}O_5Na^+$: calc. 389.2304; found 389.2302.

4-3: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.87 (m, 3H, CH_2CH_3), 1.06 (m, 1H, $CHCH_2CH_2CO$), 1.12-1.18 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.21-1.30 (m, 2H, $CH_2CH_2CH_3$), 1.30 (br. s, 1H, OH), 1.43-1.66 (m, 5H, CH_2CH_2COOMe, $CHCH_2CH_2CO$, $CH_2CH_2CH_2C{=}O$), 1.99 (t, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2CO$), 1.87-2.00 (m, 6H, $COCH_2CHO$, $CHCH_2CH_2CO$, $=CHCH_2CH_2$, $CHCH_2CH_2CO$), 2.01-2.12 (m, 3H, $CHCH_2CH{=}$, CH_2COOMe), 2.18 (m, 1H, $COCH_2CHO$), 2.50 (m, 1H, $CHCH_2CH{=}$), 2.63 (m, 1H, $CHCH_2CH{=}$), 3.36 (s, 3H, $COOCH_3$), 3.73 (dt, *J* = 5.9, 2.7 Hz, CHOH), 5.32 (m, 1H, $=CHCH_2CH_2$), 5.43 (m, 1H, $CHCH_2CH{=}$). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.2 (q, CH_2CH_3), 21.1 (t, $CH(OH)CHCH_2$), 22.9 (t, CH_2CH_3), 23.1 (t, $CHCH_2CH{=}$), 23.7 (t, $CH_2CH_2CH_2CH_3$), 24.97 (t, CH_2CH_2COOMe), 26.9 (t, $=CHCH_2CH_2$), 31.7 (t, $CH_2CH_2CH_3$), 33.30 (t, CH_2COOMe), 40.4 (t, $CHCH_2CH_2CO$), 42.6 (t, $CH_2CH_2CH_2CO$), 44.9 (t, $COCH_2CHO$), 46.7 (d, $CH(OH)CHCH_2$), 50.6 (d, $CHCH_2CH{=}$), 51.02 (q, $COOCH_3$), 70.5 (d, CHOH), 128.4 (d, $CHCH_2CH{=}$), 130.4 (d, $=CHCH_2CH_2$), 173.6 (s, COOMe), 208.4 (s, C=O), 215.0 (s, C=O).

4-4 methyl ester: ^{1}H NMR (600 MHz, C_6D_6): δ = 0.87 (m, 3H, CH_2CH_3), 1.12-1.18 (m, 2H, $CH_2CH_2CH_3$), 1.21-1.30 (m, 2H, CH_2CH_3), 1.43-1.66 (m, 7H, $CHCH_2CH_2CO$, $CH_2CH_2CH_2CO$, CH_2CH_2COOMe, $CHCH_2CH{=}$), 1.68 (m, 1H, $CHCH_2CH_2CO$), 1.88 (br. s, 1H, OH), 1.93 (dd, *J* = 18.3, 7.2 Hz, 1H, $COCH_2CHO$), 2.04 (t, *J* = 7.4 Hz, 2H,

$CH_2CH_2CH_2CO$), 2.01-2.12 (m, 4H, =$CHCH_2CH_2$, CH_2COOMe), 2.18 (dt, *J* = 7.0, 3.1 Hz, 2H, $CHCH_2CH_2CO$), 2.29 (ddd, *J* = 18.1, 6.8, 1.1 Hz, 1H, $COCH_2CHO$), 2.35 (m, 1H, $CHCH_2CH$=), 2.48 (m, 1H, $CHCH_2CH$=), 3.33 (s, 3H, $COOCH_3$), 3.53 (q, *J* = 6.9 Hz, 1H, *CH*OH), 5.32 (m, 1H, =$CHCH_2CH_2$), 5.38 (m, 1H, $CHCH_2CH$=). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.2 (q, CH_2CH_3), 22.9 (t, CH_2CH_3), 23.7 (t, $CH_2CH_2CH_2CH_3$), 25.05 (t, CH_2CH_2COOMe), 26.0 (t, CH(OH)$CHCH_2$), 26.7 (t, $CHCH_2CH$=), 26.8 (t, =$CHCH_2CH_2$), 31.7 (t, $CH_2CH_2CH_3$), 33.32 (t, CH_2COOMe), 39.9 (t, $CHCH_2CH_2CO$), 42.7 (t, $CH_2CH_2CH_2CO$), 47.1 (t, $COCH_2CHO$), 47.9 (d, CH(OH)*C*HCH_2), 51.08 (q, $COOCH_3$), 53.9 (d, *C*HCH_2CH=), 73.1 (d, *C*HOH), 127.7 (d, $CHCH_2CH$=), 131.1 (d, =*C*HCH_2CH_2), 173.4 (s, *C*OOMe), 209.4 (s, *C*=O), 214.1 (s, *C*=O). - The NMR data of **4-4** methyl ester are in agreement with those of the methyl ester synthesised from commercially available 13,14-dihydro-15-oxo-PGE_2 obtained from Cayman Chemical.

Commercially available 13,14-dihydro-15-oxo-PGE_2 (Cayman Chemical):



^{1}H NMR (600 MHz, C_6D_6): δ = 0.87 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.16 (m, 2H, $CH_2CH_2CH_3$), 1.23 (m, 2H, CH_2CH_3), 1.50-1.56 (m, 6H, $CH_2CH_2CH_2CO$, $CHCH_2CH_2CO$, CH_2CH_2COOH, *C*HCH_2CH=), 1.64 (m, 2H, *C*HCH_2CH_2CO, $CHCH_2CH_2CO$), 1.93 (dd + br. s, *J* = 18.2, 7.1 Hz, 2H, $COCH_2CHOH$, O*H*), 2.05 (t, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2CO$), 2.04-2.24 (m, 6H, =$CHCH_2CH_2$, CH_2COOH, $CHCH_2CH_2CO$), 2.24-2.33 (m, 2H, $COCH_2CHO$, $CHCH_2CH$=), 2.45 (m, 1H, $CHCH_2CH$=), 3.51 (q, *J* = 6.9 Hz, 1H, *CH*OH), 5.30 (m, 1H, =*CH*CH_2CH_2), 5.44 (m, 1H, $CHCH_2CH$=). - ^{13}C NMR (150 MHz, C_6D_6): δ = 14.2 (q, CH_2CH_3), 22.8 (t, CH_2CH_3), 23.7 (t, $CH_2CH_2CH_2CH_3$), 24.8 (t, CH_2CH_2COOH), 26.2 (t, CH(OH)$CHCH_2$), 26.6 (t, *C*HCH_2CH=), 26.7 (t, =$CHCH_2CH_2$), 31.7 (t, $CH_2CH_2CH_3$), 33.0 (t, CH_2COOH), 40.1 (t, $CHCH_2CH_2CO$), 42.8 (t, $CH_2CH_2CH_2CO$), 47.1 (t, $COCH_2CHOH$), 48.0 (d, CH(OH)*C*HCH_2), 54.1 (d, *C*HCH_2CH=), 73.1 (d, *C*HOH), 127.6 (d, $CHCH_2CH$=), 130.9 (d, =*C*HCH_2CH_2), 177.1 (s, *C*OOH), 210.5 (s, *C*=O), 214.1 (s, *C*=O).

Methylation of 13,14-dihydro-15-oxo-PGE_2:

To a solution of 1 mg (0.0028 mmol) of 13,14-dihydro-15-oxo-PGE_2 in 1.8 mL dry THF/MeOH 8:1 40 μL of a 2*M* solution of trimethylsilyldiazomethane (0.08 mmol, 28 equiv.) in diethyl ether was added at room temperature. After 30 minutes of stirring at the same

temperature the reaction mixture was evaporated in vacuum. A 600 MHz NMR spectrum of the crude product was recorded. The NMR data are in agreement with those of synthesised **4-4**.

Table 6.10 Significant NMR data and multiplicities of compounds **4-99**, **4-100**, **4-101**, **4-3** and **4-4**

Product	H8	H9	H11	H12	H13	H14	H15
15α-**4-99**	2.98 (ddd)	-	4.25 (m)	3.22 (m)	4.96 (dd)	5.75 (dd)	4.13 (dt)
15β-**4-99**	2.95 (dt)	-	4.33 (dt)	3.16 (t)	5.30 (dd)	5.72 (dd)	4.25 (m)
4-100a major	2.87 (m)	-	4.03 (m)	2.93 (m)	5.17 (dd)	5.65 (dd)	4.19 (m)
4-100a minor	2.79 (m)	-	4.09 (m)	2.93 (m)	5.13 (dd)	5.69 (dd)	4.19 (m)
4-100b	1.63 (m)	-	3.59 (dt)	2.85 (m)	5.24 (dd)	5.73 (dd)	4.25 (m)
4-101a	2.68 (dt)	-	3.86 (dt)	2.84 (ddd)	6.54 (dd)	6.18 (dd)	-
4-101b	1.61 (m)	-	3.48 (m)	2.78 (dt)	6.63 (dd)	6.24 (dd)	-
4-101c	2.25 (m)	-	3.79 (t)	2.73 (ddd)	6.91 (dd)	Not assigned	-
4-3	2.63 (m)	-	3.73 (dt)	1.87-2.00 (m)	1.06 (m), 1.43-1.66 (m)	1.87-2.00 (m)	-
4-4	1.43-1.66 (m)	-	3.53 (q)	1.69 (m)	1.43-1.66 (m)	2.18 (dt)	-
	C8	C9	C11	C12	C13	C14	C15
15α-**4-99**	49.9 (d)	213.9 (s)	72.6 (d)	52.9 (d)	127.2 (d)	138.6 (d)	85.8 (d)
15β-**4-99**	50.8 (d)	213.6 (s)	73.1 (d)	52.1 (d)	128.6 (d)	137.5 (d)	85.2 (d)
4-100a major	50.7 (d)	213.6 (s)	71.9 (d)	51.4 (d)	128.3 (d)	137.5 (d)	85.2 (d)
4-100a minor	49.9 (d)	213.9 (s)	71.6 (d)	52.1 (d)	127.8 (d)	137.9 (d)	85.6 (d)
4-100b	53.6 (d)	211.3 (d)	72.1 (d)	52.5 (d)	131.0 (d)	137.2 (d)	85.5 (d)
4-101a	50.2 (d)	212.8 (s)	71.2 (d)	51.5 (d)	140.8 (d)	133.3 (d)	198.4 (s)
4-101b	52.6 (d)	210.3 (d)	71.6 (d)	52.6 (d)	144.2 (d)	132.2 (d)	198.4 (d)
4-3	50.6 (d)	215.0 (s)	70.5 (d)	46.7 (d)	21.1 (t)	40.4 (t)	208.4 (s)
4-4	53.9 (d)	214.1 (s)	73.1 (d)	47.9 (d)	26.0 (t)	39.9 (t)	209.4 (d)

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